PRODUCT MONOGRAPH

PrTARO- RABEPRAZOLE

Rabeprazole Sodium Enteric-Coated Tablets

10 mg and 20 mg

H^+, K^+-ATPase Inhibitor

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PrTARO-RABEPRAZOLE

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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	Enteric-Coated Tablets: 10 mg and 20 mg	calcium hydroxide, dibutyl sebacate, ferric oxide red (only for 10 mg), ferric oxide yellow, hypromellose, hypromellose phthalate, low-substituted hydroxypropyl cellulose, mannitol, sodium stearyl fumarate, talc, titanium dioxide. Composition of the Imprinting Ink (only for 10 mg): Opacode black (S-1-17860), shellac, black iron oxide (E172) and propylene glycol.

INDICATIONS AND CLINICAL USE

TARO-RABEPRAZOLE (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† 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‡	**Intent-to-Treat††**
Study 604 North America	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)
Study 603 Europe	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)

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

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

†† Patients were included in the analysis if they had documented *H. pylori* infection at baseline defined as a positive ^{13}C-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).
Co-administration with rilpivirine is contraindicated.

WARNINGS AND PRECAUTIONS

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with TARO-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 international normalized ratio (INR) and prothrombin time in patients receiving proton pump inhibitors (PPIs), 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.

Antibiotic Combination Therapy

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

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

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management

with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

***Clostridium difficile*-Associated Diarrhea**

Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors can lead to an increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and *Clostridium difficile*.

An increased risk for *Clostridium difficile* infection (CDI) and *Clostridium difficile*-associated diarrhea (CDAD) has been observed in association with PPI use in several observational studies. CDI/CDAD should be considered in the differential diagnosis for diarrhea that does not improve. Additional risk factors for CDI and CDAD include recent hospitalization, the use of antibiotics, old age and the presence of co-morbidities.

Patients should be prescribed PPIs at the lowest dose and for the shortest duration required for the condition being treated and be reassessed to ascertain whether continued PPI therapy remains beneficial.

Concomitant Use with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at a high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Cyanocobalamin (Vitamin B_{12}) Deficiency

The prolonged use of proton pump inhibitors may impair the absorption of protein-bound vitamin B_{12} and may contribute to the development of cyanocobalamin (vitamin B_{12}) deficiency.

Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received a high-dose (defined as multiple daily doses) and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Interference with Laboratory Tests

During treatment with antisecretory drugs, chromogranin A (CgA) increases due to decreased gastric acidity. Increased CgA levels may interfere with investigations for neuroendocrine tumours. To avoid this interference, TARO-RABEPRAZOLE treatments should be stopped 14 days before CgA measurements (see DRUG INTERACTIONS).

Drug Interactions with Antiretroviral Drugs
PPIs have been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. A change in gastric pH may change the absorption of the antiretroviral drug. Other possible mechanisms are via CYP 2C19.

Rilpivirine:
Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see CONTRAINDICATIONS.)

Atazanavir and Nelfinavir:
Co-administration with atazanavir or nelfinavir is not recommended due to decreased atazanavir and nelfinavir exposure (see the REYATAZ and VIRACEPT Product Monographs).

If the combination of TARO-RABEPRAZOLE with atazanavir is judged unavoidable, close clinical monitoring is recommended in combination with the use of 400 mg atazanavir/100 mg ritonavir dose; the dose of TARO-RABEPRAZOLE should not exceed an equivalent dose of omeprazole of 20 mg daily (see REYATAZ Product Monograph).

Saquinavir:
If TARO-RABEPRAZOLE is co-administered with saquinavir/ritonavir, caution and monitoring for potential saquinavir toxicities including gastrointestinal symptoms, increased triglycerides, deep vein thrombosis and QT prolongation, are recommended. Dose reduction of saquinavir should be considered from the safety perspective for individual patients (see INVIRASE Product Monograph).

Endocrine and Metabolism
Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

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

The chronic use of PPIs may lead to hypomagnesemia. Moreover, hypokalemia and hypocalcemia have been reported in the literature as accompanying electrolyte disorders.

Gastrointestinal
Fundic gland polyps: As with other PPIs, long-term use of TARO-RABEPRAZOLE is associated with an increased risk of fundic gland polyps (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). Most fundic gland polyps are asymptomatic. Patients with large or ulcerated polyps may be at risk of gastrointestinal bleeding or small intestinal blockage. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Hepatic/Biliary/Pancreatic
For patients with severe liver disease, dosage adjustment should be considered.

Immune
Subacute cutaneous lupus erythematosus: Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping rabeprazole. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

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. TARO-RABEPRAZOLE 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. TARO-RABEPRAZOLE 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 (> 71 years of age): Benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category may already be at high risk of osteoporosis-related fractures. If the use of PPIs is required, they should be managed carefully according to established treatment guidelines (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

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 3094 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

	Rabeprazole Sodium N=1746 (%)	Placebo N=388 (%)
Body as a Whole		
Headache	2.8	2.8
Digestive System		
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, QTc prolongation, sinus bradycardia, supraventricular tachycardia, syncope, tachycardia, thrombophlebitis, thrombosis, varicose vein, vascular disorder, ventricular extrasystoles, 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 System: anemia, ecchymosis, hypochromic anemia, lymphadenopathy.

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, benign skin neoplasm, contact dermatitis, dry skin, fungal dermatitis, herpes simplex, herpes zoster, nail disorder, pruritus, psoriasis, rash, seborrhea, skin carcinoma, skin discolouration, 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 white blood cells (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, hypomagnesemia, osteoporosis, osteoporosis-related fractures, 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.

There have been post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (See WARNINGS AND PRECAUTIONS, Immune).

Withdrawal of prolonged PPI therapy may result in a rebound acid hypersecretion (i.e aggravation of acid-related symptoms) that can occur within days to weeks following PPI withdrawal and persist for 3-11 months.

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.

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

Rilpivirine:
Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see CONTRAINDICATIONS).

Atazanavir:
Co-administration of TARO-RABEPRAZOLE with atazanavir is not recommended. Concomitant administration of omeprazole (20 or 40 mg once daily) substantially reduced plasma C_{max} and AUC of atazanavir in healthy volunteers administered atazanavir or atazanavir/ritonavir. (see REYATAZ Product Monograph).

Nelfinavir:
Co-administration of TARO-RABEPRAZOLE with nelfinavir is not recommended. Concomitant administration of omeprazole (40 mg daily) with nelfinavir (1250 mg twice daily) markedly reduced the AUC and C_{max} for nelfinavir (by 36% and 37%, respectively) and its active metabolite M8 (by 92% and 89%, respectively) (see VIRACEPT Product Monograph)

Saquinavir:
Co-administration of saquinavir requires caution and monitoring, along with potential dose reduction of saquinavir, due to increased saquinavir exposure and thus the risk of saquinavir-related toxicities (see the INVIRASE Product Monograph). Concomitant administration of omeprazole (40 mg daily) with saquinavir/ritonavir (1000/100 mg twice daily) increased saquinavir AUC by 82% and C_{max} by 75%.

Combination Therapy with Clarithromycin
Combination therapy consisting of rabeprazole, amoxicillin and clarithromycin resulted in increases in plasma levels of rabeprazole and 14-hydroxyclarithromycin (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.

Drug-Laboratory Interactions
During treatment with antisecretory drugs, chromogranin A (CgA) increases due to decreased gastric acidity. Increased Chromogranin A (CgA) levels may interfere with investigations for neuroendocrine tumours. To avoid this interference, TARO-RABEPRAZOLE treatment should be stopped 14 days before CgA measurements (See ACTIONS & CLINICAL PHARMACOLOGY, Pharmacodynamic Properties).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

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

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:

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

OVERDOSAGE

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

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^+, K^+-ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole 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

Pharmacodynamic Properties
During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued 14 days prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range (see WARNINGS AND PRECAUTIONS, Interference with Laboratory Tests).

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 with 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^+, K^+-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

	Rabeprazole Sodium (mg QD)			
Parameter	10	20	40	Placebo
Mean AUC_{0-24} 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

	Rabeprazole Sodium 20 mg QD		Omeprazole 20 mg QD		Placebo	
Parameter	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**
Mean AUC_{0-24} Acidity	340.8*#	176.9*†	577.1*	271.2*	925.5	862.4
Median trough pH (23-hr)[1]	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

[1]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 of treatment, the percentage of time that the esophageal was 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 tablets.

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^2) basis in patients given the recommended 20 mg/day (12.3 mg/m^2) 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 β-estradiol, thyroid-stimulating hormone (TSH), 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 β-hydroxycortisol, and testosterone.

Other Effects

In humans treated with rabeprazole sodium tablets 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 sodium 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 ≤5 mL/min/1.73 m^2), 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 three 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_{max} for clarithromycin and amoxicillin were similar during combined treatment compared to monotherapy. The rabeprazole AUC and C_{max} increased by 11% and 34%, respectively, and the 14-hydroxyclarithromycin (active metabolite of clarithromycin) AUC and C_{max} increased by 42% and 46%, respectively, during the combined treatment compared to values obtained during monotherapy. This increase in exposure to rabeprazole and 14hydroxyclarithromycin 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, 14hydroxyclarithromycin, and rabeprazole which resulted in a higher C_{max} and AUC_{0-12} 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_{max}, in EM subjects, was observed in the combination treatment when compared to monotherapy.

Table 1.6: Percent (%) Increase in Pharmacokinetic Parameters (C_{max} and AUC_{0-12}) for Extensive Metabolizers (EM) and Poor Metabolizers (PM) During Combination Therapy† vs. Monotherapy††

PHARMACOKINETIC PARAMETER		Active Substance			
		rabeprazole	clarithromycin	clarithromycin M-5 metabolite (14-hydroxyclarithromycin)	amoxicillin
% Increase C_{max} (µg/mL)	EM*	38%	11%	45%	11%
	PM*	22%	24%	67%	no interaction
% Increase AUC_{0-12} (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 in original container between 15°C and 25°C, protected from moisture and heat.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TARO-RABEPRAZOLE 10 mg are pink, round, biconvex, enteric-coated tablets, with "R10" printed on one side.

TARO-RABEPRAZOLE 20 mg are yellow, round, biconvex, enteric-coated tablets.

Composition
Each TARO-RABEPRAZOLE10 mg tablet contains: 10 mg rabeprazole sodium. Nonmedicinal Ingredients: calcium hydroxide, dibutyl sebacate, ferric oxide red, ferric oxide yellow, hypromellose, hypromellose phthalate, low-substituted hydroxypropyl cellulose, mannitol, sodium stearyl fumarate, talc, titanium dioxide. Composition of the Imprinting Ink: Opacode black (S-1-17860), shellac, black iron oxide (E172) and propylene glycol.

Each TARO-RABEPRAZOLE20 mg tablet contains: 20 mg rabeprazole sodium. Nonmedicinal Ingredients: calcium hydroxide, dibutyl sebacate, ferric oxide yellow, hypromellose, hypromellose phthalate, low-substituted hydroxypropyl cellulose, mannitol, sodium stearyl fumarate, talc, titanium dioxide.

TARO-RABEPRAZOLE Enteric-Coated Tablets 10 mg are available as 3 blisters x 10 tablets per box, and as bottles of 100 tablets.

TARO-RABEPRAZOLE Enteric-Coated Tablets 20 mg are available as 3 blisters x 10 tablets per box, and as bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

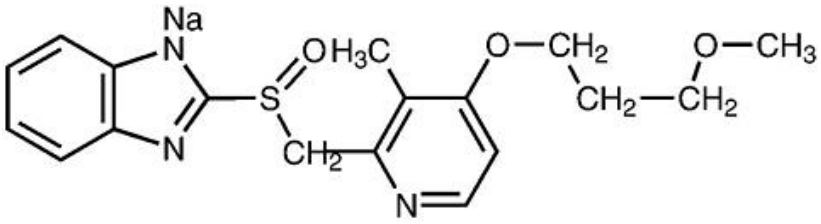
Proper Name: rabeprazole sodium

Chemical Name: 2-[[[4-(3-methoxy-propoxy)-3-methyl-2- pyridinyl] methyl]sulfinyl]-1-H benzimidazole sodium salt.

Molecular Formula: $C_{18}H_{20}N_3NaO_3S$

Molecular Mass: 381.43 g/mol

Structural Formula:



Physicochemical Properties: Rabeprazole sodium is a white to yellowish white crystalline powder and exhibits polymorphism. It is soluble in water. pH is between 10.0 and 12.0 in 1% w/v in water. pKa is 8.9.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative blind, randomized, single-dose, 3-way semi-replicate, crossover study was conducted to evaluate the bioavailability between TARO-RABEPRAZOLE 20 mg enteric-coated tablets (Sun Pharma Canada Inc.) and Pariet® 20 mg enteric-coated tablets (Janssen Ortho Inc.) after a single-dose in 46 healthy male and female subjects under fasting conditions.

Rabeprazole (1 x 20 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval#
AUC_{0-t} (ng·h/mL)	773.87 907.06 (49.29)	774.64 870.76 (50.05)	99.90	94.71 – 105.38
AUC_{0-inf} (ng·h/mL)	800.47 925.46 (48.49)	796.48 897.72 (48.88)	100.50	95.41 – 105.86
C_{max} (ng/mL)	532.62 611.39 (38.24)	560.09 602.71 (40.02)	95.09	86.16 – 104.95
T_{max}§ (h)	3.12 (35.17)	3.57 (22.72)		
$T_{½}$ § (h)	1.82 (51.66)	1.86 (49.90)		

* TARO-RABEPRAZOLE 20 mg tablets (Sun Pharma Canada Inc.).

† Pariet® 20 mg tablets (Janssen-Ortho Inc.) were purchased in Canada.

§ Expressed as arithmetic mean (CV%) only.

Based on least-squares mean estimates.

A comparative blind, randomized, single-dose, 3-way semi-replicate, crossover study was conducted to evaluate the bioavailability between TARO-RABEPRAZOLE 20 mg enteric-coated tablets (Sun Pharma Canada Inc.) and Pariet® 20 mg enteric-coated tablets (Janssen Ortho Inc.) after a single-dose in 43 healthy male and female subjects under fed conditions.

Rabeprazole (1x 20 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval#
AUC_{0-t} (ng·h/mL)	641.75 833.60 (68.84)	637.34 744.77 (60.73)	100.69	91.14 – 111.24
AUC_{0-inf} (ng·h/mL)	640.21 830.66 (71.25)	650.34 767.81 (62.43)	98.44	88.67 – 109.30
C_{max} (ng/mL)	330.00 448.86 (59.38)	338.29 409.01 (50.41)	97.55	81.05 – 117.41
T_{max}§ (h)	10.19 (57.28)	10.93 (55.32)		
$T_{½}$§ (h)	2.57 (81.52)	2.82 (98.89)		

* TARO-RABEPRAZOLE 20 mg tablets (Sun Pharma Canada Inc.).

† Pariet® 20 mg tablets (Janssen-Ortho Inc.) were purchased in Canada.

§ Expressed as arithmetic mean (CV%) only.

Based on least-squares mean estimates.

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	Rabeprazole Sodium 20 mg 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 night time (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	Rabeprazole Sodium 20 mg QD	Placebo
	N=159	N=160	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 ($p\leq0.003$) 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 RAB-USA-2

	Placebo n (%)†	**Rabeprazole 10 mg QD n (%)†**	**Rabeprazole 20 mg QD n (%)†**
Intent-To-Treat (ITT) population	N=68	N=64	N=67
Per-Protocol (PP) population	N=61	N=59	N=58
Complete Heartburn Relief			
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)
Satisfactory Heartburn Relief			
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)

† Analysis based on ITT population

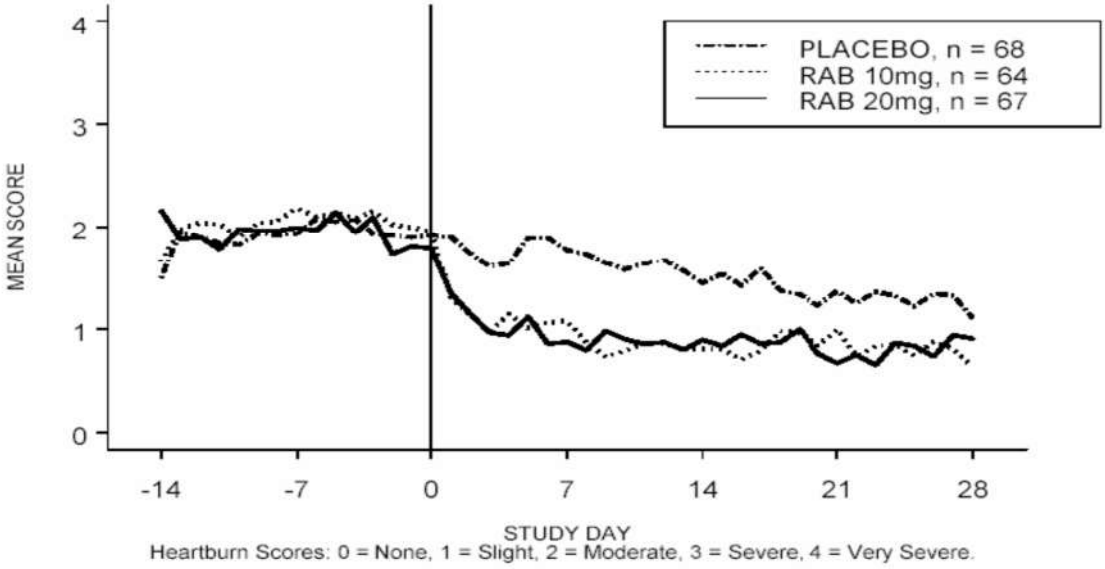
Table 2.6: Complete Relief of Heartburn and Satisfactory Relief of Heartburn Frequency from Study RAB-USA-3

	Placebo n (%)†	**Rabeprazole 20 mg QD n (%)†**
Intent-To-Treat (ITT) population	N=58	N=59
Per-Protocol (PP) population	N=45	N=45
Complete Heartburn Relief		
Double-blind Week 2	2 (3.4)	13 (22.0)
Double-blind Week 4	2 (3.4)	17 (28.8)
Satisfactory Heartburn Relief		
Double-blind Week 2	15 (25.9)	33 (55.9)
Double-blind Week 4	12 (20.7)	30 (50.8)

† Analysis based on ITT population

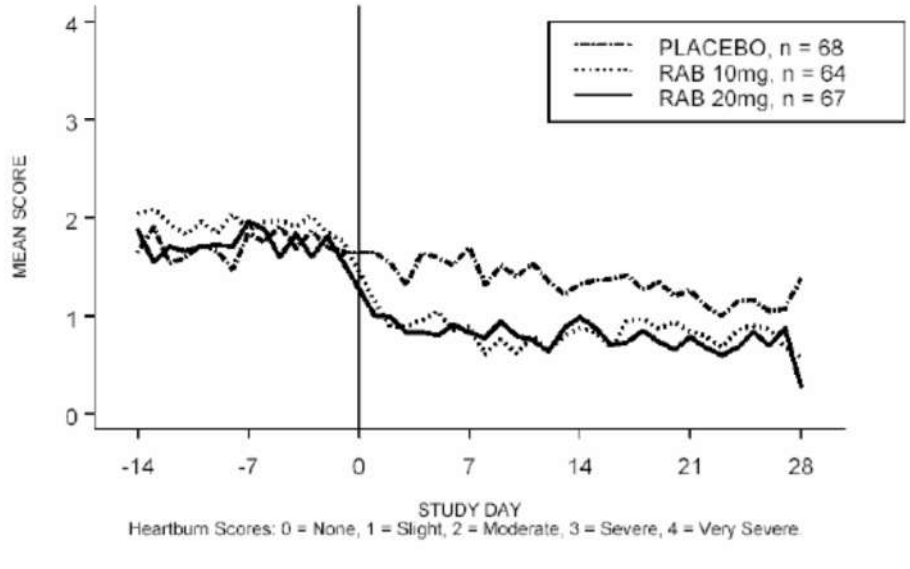
The mean decreases from baseline in average daytime and nighttime heartburn scores were significantly greater for rabeprazole 20 mg as compared to placebo at week 4. Graphical displays depicting the daily mean daytime and nighttime scores are provided in Figures 1 to 4.

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

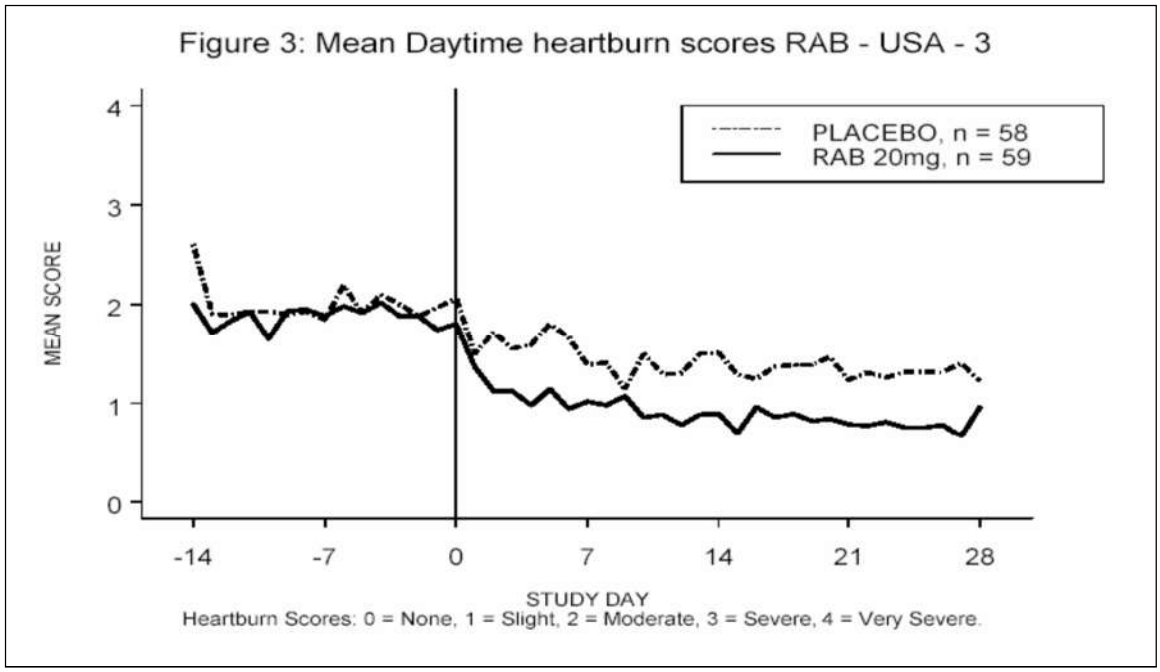


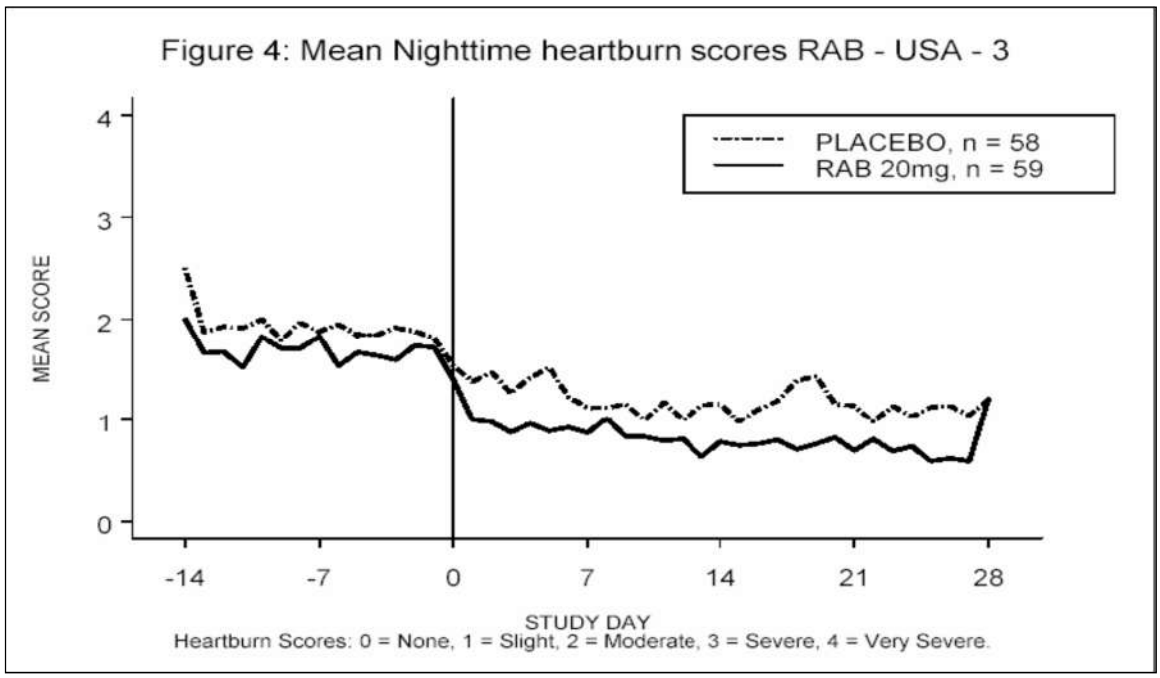
Heartburn Scores: 0 = None, 1 = Slight, 2 = Moderate, 3 = Severe, 4 = Very Severe.

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



Heartburn Scores: 0 = None, 1 = Slight, 2 = Moderate, 3 = Severe, 4 = Very Severe.





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 ^{13}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 ^{13}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 sodium doses from 20 to 120 mg for up to 12 months. Rabeprazole sodium 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 sodium 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.

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_{50} values for rabeprazole sodium on gastric acid secretion are summarized in Table 2.11, below.

Table 2.11: Rabeprazole Sodium ED_{50} Value for the Inhibition of Gastric Acid Secretion

Species	Model	Acid Secretion	ED_{50} (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_{50} values for rabeprazole sodium on the anti-ulcer activity are summarized in Table 2.12.

Table 2.12: Rabeprazole Sodium ED_{50} Value for the Anti-Ulcer Effect

Species	Ulcerogenesis Model	ED_{50} (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 (IM), 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 PO (1.5 mg/kg, in water) or IV (1.5 mg/kg, in saline) to the Beagle dog. The same differences were seen after co-administration of the RS-(") racemate, both PO and IV (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 IV 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, IV) produced pharmacokinetic results comparable to those when R(+)-rabeprazole sodium and S(-)-rabeprazole sodium were administered separately (20 mg/kg, IV). 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 mcg-equiv/g by Day 28. In another study, tissue distribution was similar after PO and IV 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 IV 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}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}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 IV administration of a 5 mg/kg dose of ^{14}C-rabeprazole to SD rats, the highest levels of ^{14}C were observed in the gastric mucosa, followed in descending order by glandular stomach, kidney, bladder, liver, hematocytes, small intestine and thyroid. The highest levels of ^{14}C-rabeprazole after 168 hours were found in hematocytes.

Similar patterns of tissue distribution of radioactivity, depletion kinetics, and metabolic profile of ^{14}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}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}C-rabeprazole (0.01% to 1.16% of administered dose) was observed in fetal tissues after administration of ^{14}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}C-rabeprazole to lactating females on the 14th 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}C-Urea Breath Test (^{13}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 24hour 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 Intragastric 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[a] % Time pH>4	84.96	64.09	12.90	5.62
Mean[a] % Time pH>3	91.89	77.42	23.24	18.72
AUC[b] over 24 hrs	26.91	105.45	604.34	694.14

[a] Mean is the adjusted mean from ANOVA

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

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes: For the U.S. 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[a] for Triple Therapy - Intent to Treat

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

[a] Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results.

[b] Susceptible (S) MIC ≤0.25 μg/mL, Intermediate (I) MIC = 0.5 μg/mL, Resistant (R) MIC ≥ 1 μg/mL

Patients 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 re-treated 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 ≤ 0.25 μg/mL) to amoxicillin at baseline. The other 2 patients had baseline *H.pylori* isolates with an amoxicillin MIC of 0.5 μg/mL, and both isolates were clarithromycin-resistant at baseline; in one case the *H. pylori* was eradicated. In the 7- and 10-day treatment groups, respectively, 75% (107/145) and 79% (112/142) of the patients who had pretreatment amoxicillinsusceptible MICs (≤ 0.25 μg/mL) were eradicated of *H.* pylori. No patients developed amoxicillinresistant *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_{50} was 1.6 and the MIC_{90} 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_{50} in mice and rats was ≥1000 mg/kg; the intravenous LD_{50} in mice and rats was ≥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_{50} or NOEL	
					M	F
Mouse/ICR (Oral route: fasted 19-22 hrs prior to dosing; IV route: *ad libitum* feeding	5 per sex per group	PO (gavage)/ purified water IV/ physiological saline	Male: 629, 786, 983, 1229, 1536, 1920 and 2400 mg/kg Female: 629, 786, 983, 1229, 1536, 1920, 2400 and 3000 mg/kg Male: 131, 164, 205, 256, and 320 mg/kg Female: 164, 205, 229, 256, and 320 mg/kg	Single dose	1206 220	1012 237
Rat/Slc: SD (oral route: fasted 17-24 hrs prior to dosing; IV route: *ad libitum* feeding)	5 per sex per group	PO (gavage)/ purified water IV/ physiological saline	Male: 819, 1024, 1280, 1431, 1600 and 2000 mg/kg Female: 655, 819, 1024, 1280, 1600 and 2000 mg/kg Male: 98, 123, 154, 172 and 192 mg/kg Female: 98, 123, 154, 192, 240 and 300 mg/kg	Single dose	1447 157	1322 152
Rat Slc:SD (*ad libitum* feeding)	5 per sex per group	IV/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/Slc: SD (animals were fasted overnight)	5 per sex per group	Degradation Products I and II and Impurity PO (gavage) Metabolite IV/ 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 (*ad libitum* feeding)	1 per sex per group	PO (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 mg/kg [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 including increases in stomach weight, gastric mucosal and nonmucosal mass, and ECL hypertrophy and/or 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 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_2-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 fundic 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 luteinizing 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_1 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 are 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 mcg/mL in the activated test. A weak response for mutagenicity was observed at concentrations ranging from 90 to 110 mcg/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 $TK^{+/-}$ cells when testing in the absence of metabolic activation, but was weakly positive when tested at concentrations of 25 and 30 mcg/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^2] basis for patients given the recommended 20 mg/day [12.3 mg/m^2] 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^2] basis for patients given the recommended 20 mg/day [12.3 mg/m^2] 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^2] basis for patients given the recommended 20 mg/day [12.3 mg/m^2] 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. (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 tumour 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.

REFERENCES

1. Chiku S, Nakata H, Ishikawa T, Yuzuriha T. Pharmacokinetics of a new benzimidazole sulfoxide derivative, E3810 (1): Pharmacokinetics in rats and dogs. Yakubutsu Dotai (JSSX Journal) 1994; 9(5): 603-611.

2. Chiku S, Yoshimra T, Nakata H, Yuzuriha T. Pharmacokinetics of a new benzimidazole sulfoxide derivative, E3810 (2): Absorption, distribution, metabolism and excretion in rats. Yakubutsu Dotai (JSSX Journal) 1994; 9(5): 612-627.

3. Danks A, Holmes P, Sparrow S, Virgo DM, Aloki T, Hayakawa K, et al. 52-week oral (capsule) toxicity study with 26-week reversibility period in dogs with E3810. GI Research 1993;1(5):574-600.

4. Fujusaki H, Shibata H, Okentani K, Murakami M, Fujimoto M, Wakabayashi T, et al. Inhibitions of acid secretion by E3810 and omeprazole, and their reversal by glutathione. Biochem Pharmacol 1991; 42(2):321-8.

5. Ishizaki T, Chiba K, Manabe K, Koyama E, Hayashi M, Yasuda S, et al. Comparison of the interaction potential of a new proton pump inhibitor, E3810, versus omeprazole with diazepam in extensive and poor metabolizers of S-mephenytoin 4'-hydroxylation. Clin Pharmacol Ther 1995;58(2):155-64.

6. Matsumoto N, Murakami Y, Komatsu H, Toge K, Yamazaki M, Kawamoto T, et al. Effect of proton pump inhibitor, E3810 on intragastric pH. Proceedings of the Japanese Soc of Gastric Secretion Research 1991; 23:1-5.

7. Miner P Jr., Orr W, Filippone J, Jokubaitis L, Sloan S. Rabeprazole in nonerosive gastroesophageal reflux disease: A randomized placebo-controlled trial. Am J Gastroenterol 2002; 97(6):1332-1339.

8. Miyazaki Y, Imamura I, Yasunaga Y, Shinomura M, Fukui H, Wada H, et al. Effects of potent acid secretion inhibitors on gastrin secretion and histamine metabolism in the gastric mucosa. A study with the proton pump inhibitor E3810. Bulletin of Symposium of Gastric Secretion 1992; 24:93-6.

9. Miwa H, Yamada T, Sato K, Ohta K, Ohkura R, Murai T, Nagahara A, Takei Y, Ogihara T, Sata N. Efficacy of reduced dosage of rabeprazole in PPI/AC therapy for *Helicobacter pylori* infection: Comparison of 20 and 40 mg rabeprazole with 60 mg lansoprazole. *Digestive Diseases and Sciences* 2000; 45(1):77-82.

10. Miwa H, Ohkura R, Murai T, Sato K, Nagahara A, Hirai S, Watanabe S, Sato N. Impact of rabeprazole, a new proton pump inhibitor, in triple therapy for *Helicobacter pylori* infection. Comparison with omeprazole and lansoprazole. *Alimentary Pharmacology & Therapeutics* 1999; 13(6):741-746.

11. Morii M, Takata H, Fujisaki H, Takeguchi N. The potency of substituted benzimidazoles such as E3810, omeprazole, Ro 18-5364 to inhibit gastric H^+, K^+-ATPase is correlated with the rate of acid-activation of the inhibitor. Biochem Pharmacol 1990; 39:661-7.

12. Morii M, Takeguchi N. Different biochemical modes of action of two irreversible H^+, K^+-ATPase inhibitors, omeprazole and E3810. J Biol Chem 1993; 268(29):21553-9.

13. Noguchi M, Nakanowatari J, Tanabe Y, Tagaya O, Aoi T, Yamatsu K, et al. E3810 toxicity study in Beagle dogs after repeated oral administration for 13 weeks followed by a 5 week recovery period. GI Research 1993; 1(5 suppl.):527-56 (59-88).

14. Ohnishi A, Yasuda S, Ogawa T, Tomono Y, Hasegawa J, Morishita N. Results of phase I studies of E3810, a new proton pump inhibitor in healthy male volunteers. Single and multiple dose study. GI Research 1993;1(5):199-207.

15. Ohnishi A, Yasuda S, Ogawa T, Tomono Y, Hasegawa J, Morishita N. E3810 phase I clinical trial results – single and repeated administrations. GI Research 1993;1(5):667-75.

16. Okada F, Osumi I, Kawaguchi T, Yamatsu K, Igarashi T. Fetal organogenesis study in rabbits treated intravenously with E3810. GI Research 1993; 1 (5 suppl.): 647-54 (179-86).

17. Osumi I, Goto M, Okada F, Matsubara Y, Yamatsu K, Igarashi T. Fetal organogenesis study in rats treated orally with E3810. GI Research 1993; 1 (5 suppl.): 615-32 (147-64).

18. Shmizu M, Uto K, Kobayashi Y, Yamashita Y, Kato M, Shinoda A, et al. Perinatal and postnatal toxicity study of E3810 in rats after intravenous administration. GI Research 1993; 1 (5 suppl.): 633-46 (165-77).

19. Stack WA, Knifton A, Thirlwell D, Cockayne A, Jenkins D, Hawkey CJ, Atherton JC. Safety and efficacy of rabeprazole in combination with four antibiotic regimens for the eradication of *Helicobacter pylori* in patients with chronic gastritis with or without peptic ulceration. *American Journal of Gastroenterology* 1998; 93(10):1909-1913.

20. Storer RD, French JE, Haseman J, Jajian G, LeGrand EK, et al. p53+/- Hemizygous knockout mouse: Overview of available data. Toxicologic Pathology 2001; 29 (Suppl.): 30-50.

21. Verdu EF, Armstrong D, Fraser R *et al*. Effect of *Helicobacter pylori* status on intragastric pH during treatment with omeprazole. *Gut* 1995; 36:539-43.

22. Williams MP, Sercombe J, Hamilton MI, Pounder RE. A placebo-controlled trial to assess the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects. Aliment Pharmacol Ther 1998; 12:1079-1089.

23. Wong BCY, Wong WM, Yee YK, Hung WK, Yip AWC, Szeto M, Li KF, Lau P, Fung FMY, Tong TSM, Lai KC, Hu WHC, Yuen MF, Hui CK, Lam SK. Rabeprazole based 3-day and 7-day triple therapy versus 7-day omeprazole based triple therapy for the treatment of *Helicobacter pylori* infection. *Alimentary Pharmacology Therapeutics* 2001; 15: 1959-1965.

24. Yasuda S, Horai Y, Tomono Y, Nakai H, Yamato C, Manabe K, et al. Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephytoin 4-hydroxylation status. Clin Pharmacol Ther 1995; 58(2):143-54.

25. Yasuda S, Ohnishi A, Ogawa T, Tomono Y, Hasegawa J, Nakai H, et al. Pharmacokinetic properties of E3810, a new proton pump inhibitor, in healthy male volunteers. Int J Clin Pharmacol Ther 1994; 32:466-73.

26. Janssen Inc. Product Monograph, PARIET* (* TM Eisai Co., Ltd). Control No 220645 Date of revision: November 21, 2018.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]TARO-RABEPRAZOLE
Rabeprazole Sodium Enteric-Coated Tablets
10 mg and 20 mg

Read this carefully before you start taking TARO-RABEPRAZOLE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TARO-RABEPRAZOLE.

What is TARO-RABEPRAZOLE used for?

TARO-RABEPRAZOLE is used in adults to:
- relieve symptoms and heal duodenal ulcers.
- relieve symptoms and heal stomach ulcers.
- heal gastroesophageal reflux disease (GERD) and relieve its symptoms such as:
  - the burning feeling that rises from the chest to the throat (heartburn).
  - the flow of bitter/sour juice into the mouth (regurgitation).
- treat symptoms of non-erosive reflux disease (NERD) such as heartburn and regurgitation
- maintain longer term healing of gastroesophageal reflux disease (GERD).
- treat rare conditions where excess acid is produced in the stomach (e.g., **Zollinger-Ellison syndrome**).
- treat ulcers caused by infection with the bacterium, *Helicobacter pylori* (*H. pylori*), and prevent these ulcers from coming back by:
  - taking TARO-RABEPRAZOLE with antibiotics such as amoxicillin and clarithromycin, as directed by your doctor.
  - following the information on the antibiotics provided to you by the pharmacist.

How does TARO-RABEPRAZOLE work?
TARO-RABEPRAZOLE is a medicine called a proton pump inhibitor (PPI). TARO-RABEPRAZOLE works by reducing the amount of acid made in your stomach.

What are the ingredients in TARO-RABEPRAZOLE?
Medicinal **ingredients**: rabeprazole sodium
Non-medicinal ingredients: calcium hydroxide, dibutyl sebacate, hypromellose, hypromellose phthalate, low-substituted hydroxypropyl cellulose, mannitol, sodium stearyl fumarate, talc, titanium dioxide.

The 10 mg tablet also contains ferric oxide red and ferric oxide yellow as colouring agents. The 20 mg tablet contains ferric oxide yellow as a colouring agent.

TARO-RABEPRAZOLE comes in the following dosage forms:
Tablets of 10 mg and 20 mg

Do not use TARO-RABEPRAZOLE if you are allergic to:

- rabeprazole or other medications in this class
- the "nonmedicinal" ingredients in TARO- Rabeprazole tablets. (See What are the ingredients in TARO-RABEPRAZOLE)
    - the antibiotics amoxicillin or clarithromycin if these are used with TARO-RABEPRAZOLE to treat ulcers caused by *H. pylori*

Do not use TARO-RABEPRAZOLE if you are:

- taking rilpivirine

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TARO- Rabeprazole. Talk about any health conditions or problems you may have, including:

- all health problems you have now or have had in the past
- any liver problems
- if you experience symptoms including palpitations (rapid heartbeat), dizziness, seizures, twitching, spasms, muscle weakness, cramps and convulsions. These may be signs of low magnesium levels in your blood
- if you are taking methotrexate
- if you are pregnant or planning to become pregnant
- if you are breast-feeding or planning to breast-feed
- if you are due to have a specific blood test (Chromogranin A)

Other warnings you should know about:

Long-term use of TARO-RABEPRAZOLE may prevent normal absorption of vitamin B_{12} from the diet and could lead to vitamin B_{12} deficiency. Talk to your doctor

Using TARO-RABEPRAZOLE for a long period of time (a year or longer) may increase the risk of fractures of the hip, wrist or spine. Talk to your doctor about your risk.

Using medicines like TARO-RABEPRAZOLE for a long period of time may cause a growth in your stomach (polyp). This can lead to intestinal blockage or bleeding. Talk to your doctor if you experience nausea or stomach pain while you are taking TARO-RABEPRAZOLE.

Tell your healthcare professional about all the medicines you take, including any drugs (prescription and non-prescription), vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TARO-RABEPRAZOLE:

- ketoconazole
- digoxin
- warfarin
- antiretroviral drugs such as atazanavir, nelfinavir, saquinavir
- methotrexate

How to take TARO-RABEPRAZOLE:

- Take TARO-RABEPRAZOLE exactly as prescribed by your doctor, usually for a specific number of weeks.
- Use the lowest dose and shortest time as determined by your doctor.
- Do not stop taking TARO-RABEPRAZOLE even when you start to feel better. If you stop taking TARO-RABEPRAZOLE too soon, your symptoms may return.
- Take TARO-RABEPRAZOLE with or without meals
- Swallow tablets whole with a liquid. Do not chew or crush the tablets.
- Talk to your doctor **If you have** any concerns.

Usual dose:

Condition	Adult Dose	How often	How long
reflux symptoms with esophagitis	20 mg	once daily	four weeks
reflux symptoms without esophagitis, such as heartburn and regurgitation	10 mg to a maximum of 20 mg	once daily	four weeks
duodenal ulcer	20 mg	once daily	Up to four weeks
stomach ulcer	20 mg	once daily	Up to six weeks
ulcer caused by *H. pylori* infection[†]	20 mg	twice daily in combination with antibiotic drugs (clarithromycin and amoxicillin) preferably with the morning and evening meals	one week

[†]If you are given TARO-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:

If you think you have taken too much TARO-RABEPRAZOLE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take one dose of TARO-RABEPRAZOLE 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.**

What are possible side effects from using TARO-RABEPRAZOLE?

Like all medicines, TARO-RABEPRAZOLE can cause side effects.

Headache and diarrhea are the most common side effects experienced with TARO-RABEPRAZOLE. Less common side effects are rash, itchiness and dizziness. If any of these become troublesome, consult your doctor.

Treatment in combination with antibiotics: If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have *Clostridium difficile colitis* (bowel inflammation). If this occurs, stop taking TARO-RABEPRAZOLE and contact your healthcare professional immediately.

If you experience symptoms of low magnesium levels in your body, your doctor may stop TARO-RABEPRAZOLE.

Tell your doctor right away if you have any of these symptoms:

- seizures.
- dizziness.
- abnormal or fast heart beat.
- jitteriness.
- jerking movements or shaking (tremors).
- muscle weakness.
- spasms of the hands and feet.
- cramps or muscle aches.
- spasm of the voice box.
- a fracture (broken bone).
- New or worsening joint pain.
- Rash on your cheeks or arms that gets worse in the sun.
- Blood in stool.

Stopping your PPI therapy after taking it for a long time, may cause your symptoms to get worse and your stomach may increase acid production. Carefully follow your doctor's instructions when discontinuing your PPI therapy.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store in original container between 15°C and 25°C, protected from moisture and heat.
Keep out of the sight and reach of children.

If you want more information about TARO-RABEPRAZOLE:

- Talk to your healthcare professional.
- For questions or concerns contact the manufacturer, Sun Pharma Canada Inc.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by contacting the sponsor, Sun Pharma Canada Inc., at: 1-866-840-1340.

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