PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]JAMP Rabeprazole

Rabeprazole Sodium Delayed Release Tablets

Delayed Release Tablets, 10 mg and 20 mg rabeprazole sodium (as rabeprazole sodium hydrate), Oral

Proton Pump Inhibitor

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.5 Missed Dose	03/2023

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Sections or subsections that are not applicable at the time of authorization are not listed

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

JAMP Rabeprazole (rabeprazole sodium delayed release tablets) is indicated for treatment of conditions where a reduction of gastric acid secretion is required, such as:

- Symptomatic relief and healing of erosive or ulcerative gastroesophageal refluxdisease (GERD).
- Long-term maintenance of healing of erosive or ulcerative gastroesophageal refluxdisease (GERD).
- Treatment of symptoms (i.e., heartburn and regurgitation) in symptomatic gastroesophageal reflux disease (GERD), also called non-erosive reflux disease(NERD).
- Symptomatic relief and healing of duodenal ulcers.
- Symptomatic relief and healing of gastric ulcers.
- Long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.
- Eradication of Helicobacter pylori (H. pylori) associated with duodenal ulcer disease (active or history within the past 5 years). Rabeprazole, in combination with appropriate antibacterial therapeutic regimens such as amoxicillin and clarithromycin, is indicated for the treatment of patients with duodenal ulcer disease associated with H. pylori infection. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence. See 14.1 Clinical Trials by Indication, H. pylori Eradication and Product Monographs for amoxicillin and clarithromycin.

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of rabeprazole have not been established in children under the age of 18 years; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>71 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of rabeprazole in geriatric patients has been established. Therefore, Health Canada has authorized all indications for geriatric use. No dosage adjustment is necessary for elderly patients. See 7.1.4 Geriatrics

2. CONTRAINDICATIONS

- JAMP Rabeprazole is contraindicated in 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 6 DOSAGE FORMS, COMPOSITION AND PACKAGING
- When JAMP Rabeprazole is used in combination with other antibacterial regimens for the eradication of H. pylori, the contraindications for those antibiotics such as amoxicillin and clarithromycin, as found in the corresponding Product Monographs, should be considered.
- JAMP Rabeprazole is contraindicated with co-administration of rilpivirine. See 7 WARNINGS AND PRECAUTIONS and 9.4 Drug-Drug Interactions.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients should use the lowest dose and shortest duration of proton pump inhibitor (PPI) therapy appropriate to the conditionbeing treated.

4.2 Recommended Dose and Dosage Adjustment

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

The recommended adult oral dose is 20 mg once daily (QD) . 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

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

10 mg QD has been demonstrated to be effective versus placebo in the maintenance of healingof GERD. The maximum recommended adult oral dose is 20 mg QD

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

The recommended adult oral dose is 10 mg QD to a maximum of 20 mg QD in patientswith NERD. If symptom control is not achieved after four weeks, further investigation is recommended

Symptomatic Relief and Healing of Duodenal Ulcers

The recommended adult oral dose is 20 mg QD for up to four weeks. 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 QD for up to six weeks 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 improvementachieved after three weeks for most patients.

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

The JAMP Rabeprazole dosage in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg QD. 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 two times a day (BID) have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with JAMP Rabeprazole tablets for up to one year.

Eradication of H. pylori Associated with Duodenal Ulcer Disease – Triple Therapy

JAMP Rabeprazole	20 mg	Twice Daily (BID) for 7 Days
Amoxicillin	1000 mg	BID for 7 Days
Clarithromycin	500 mg	BID for 7 Days

All three medications should be taken BID 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.

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.

Health Canada has not authorized an indication for pediatric use. See 1.1 Pediatrics.

4.4 Administration

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

4.5 Missed Dose

If a dose of JAMP Rabeprazole is missed, the patient should be instructed to take the dose as soon aspossible. However, if the next scheduled dose is due soon, the patient should not take the missed dose, and should be instructed to take the next dose on time. Patients should be instructed not to take two doses at one time to make up for a missed dose.

5 OVERDOSAGE

There has been no experience with large overdoses of rabeprazole although seven reports of accidentaloverdosage with rabeprazole have been received. The maximum established exposure has not exceeded 60 mg BID or 160 mg QD. 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients

Oral	Tablet (delayed-release),10 mg, 20 mg of rabeprazole sodium (as rabeprazole sodium hydrate).	Diethyl Phthalate, Ethyl Cellulose (7 cps), Ferric Oxide Red, Ferric Oxide Yellow, Hypromellose Phthalate, Mannitol, Magnesium Oxide, Magnesium Stearate, Povidone,Sodium Starch Glycolate, Talc, Titanium Dioxide and black ink (shellac glaze, iron oxide black and propylene glycol).

JAMP Rabeprazole 10 mg: Pink colored, round biconvex, delayed release tablets imprinted with 'R10' on one side in black ink and plain on other side; are available in HDPE bottles of 100 and 500 tablets.

JAMP Rabeprazole 20 mg: Yellow colored, round biconvex, delayed release tablets imprinted with 'R20' on one side in black ink and plain on other side; are available in HDPE bottles of 100 and 500 tablets.

7 WARNINGS AND PRECAUTIONS

General

Gastric Malignancy

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with JAMP Rabeprazole is instituted, as treatment with rabeprazole may alleviate symptoms and delay diagnosis. Symptomatic response to therapy with JAMP Rabeprazole does not preclude the presence of gastric malignancy.

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, itis 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 (C. 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 drugalone. 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 *C. 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, Campylobacter* and *C. 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, oldage 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 Warfarin

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 (PTT) in patients receiving PPIs, including rabeprazole, and warfarin concomitantly. Increases in INR and PTT may lead to abnormal bleeding and even death.

Patients treated with a PPI and warfarin concomitantly may need to be monitored for increases in INR and PTT (See 9 DRUG INTERACTIONS).

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 (See 9 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 theabsorption of the antiretroviral drug. Other possible mechanisms are via CYP2C19 (See 9 DRUG INTERACTIONS).

Rilpivirine:

Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see 2 CONTRAINDICATIONS).

Atazanavir and Nelfinavir:

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

If the combination of JAMP 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 JAMP Rabeprazole should not exceed an equivalent dose of omeprazole of 20

mg QD (see REYATAZ Product Monograph).

Saquinavir:

If JAMP 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

Cyanocobalamin (Vitamin B12) Deficiency
The prolonged use of PPIs may impair the absorption of protein-bound vitamin B12 and may contribute to the development of cyanocobalamin (vitamin B12) deficiency.

Hypomagnesemia:

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely inpatients 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 throughout treatment (see 8.5 Post-Market Adverse 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 rabeprazole is associated with anincreased risk of fundic gland polyps (see 8.5 Post-Market Adverse DrugReactions). Most fundic gland polyps are asymptomatic. Patients with large or ulcerated polyps maybe 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.

Monitoring and Laboratory Tests

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, JAMP Rabeprazole treatments should be stopped 14 days

before CgA measurements (see 9.7 Drug-Laboratory Test Interactions).

Musculoskeletal

Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received 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 4.2 Recommended Dose and Dosage Adjustment and 8.5 Post-Market Adverse Reactions).

Renal

No dosage adjustment is necessary in patients with renal insufficiency.

Skin

Subacute Cutaneous Lupus Erythematosus (SCLE)

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 8.5 Post-Market Adverse Reactions).

7.1 Special Populations

7.1.1 Pregnant Women

The safety of rabeprazole treatment in pregnancy has not been established. JAMP Rabeprazole tablets should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus.

7.1.2 Breast-feeding

It is not known whether rabeprazole is excreted in human milk. JAMP Rabeprazole tablets should not be given to nursing mothers unless the expected benefits outweighthe potential risks to the infant.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Geriatrics (> 71 years of age): Benefits of PPI use 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 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, Musculoskeletal, Bone Fracture and 8.5 Post-Market Adverse Reactions).

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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Worldwide, over 3,094 patients have been treated with rabeprazole 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. The majority of adverse events experienced during clinical studies were mild or moderate in severity and transient in nature. The most frequently reported adverse drug reactions with rabeprazole in the North American placebo-controlled clinical trials were headache (3%) and diarrhea (3%). Other reported adverse reactions were abdominal pain, flatulence, constipation, dry mouth and dizziness each reported in 1% of patients and rash in < 1% of patients.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, 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 reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

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

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.

8.3 Less Common Clinical Trial Adverse Reactions

In short- and long-term studies, the following adverse events were reported in <1% of the patients treated with rabeprazole 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.
CardiovascularSystem:	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.
MusculoskeletalSystem:	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 discoloration, skin hypertrophy, skin melanoma, skin nodule, sweating, urticaria.
Special Senses:	abnormal vision, amblyopia, blepharitis, blurry vision, cataract, conjunctivitis , corneal opacity, deafness, diplopia, dry eyes, ear disorder, ear pain, eye disorder, eye hemorrhage, eye pain, glaucoma, lacrimation disorder, otitis externa, otitis media, retinal degeneration, retinal disorder, strabismus, taste perversion, tinnitus, vestibular disorder, vitreous disorder.
Urogenital System:	breast enlargement, breast neoplasm, breast pain, cystitis, dysmenorrhea, dysuria, hematuria, impotence, kidney calculus, leukorrhea, mastitis, menorrhagia, menstrual disorder, metrorrhagia, orchitis, polycystic kidney, polyuria, prostatic disorder, urinary frequency, urinary incontinence, urinary tract disorder, uterine hemorrhage, vaginal hemorrhage, vaginitis.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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

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.

8.5 Post-Market Adverse Reactions

Blood and lymphatic system disorders	Agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, neutropenia
General disorder and administration site conditions	Sudden death
Hepatobiliary disorders	Jaundice, hepatitis, hepatic encephalopathy (in patients with underlying cirrhosis)
Immune system disorders	Anaphylaxis, hypersensitivity reactions (facial swelling, hypotension, dyspnea)
Investigations	TSH increased, hepatic enzymes increased
Metabolism and nutrition disorders	Hyperammonemia, hypomagnesemia
Musculoskeletal and connective tissue disorders	Rhabdomyolysis, osteoporosis, fracture due to osteoporosis, myalgia, arthralgia
Nervous system disorders	Coma
Psychiatric disorders	Disorientation, delirium
Renal and urinary disorders	Interstitial nephritis
Reproductive system and breast disorders	Gynecomastia
Respiratory, thoracic and mediastinal disorders	Interstitial pneumonia
Skin and subcutaneous tissue disorders	Angioedema, bullous drug eruption, other drug eruptions, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome

There have been post-marketing reports of SCLE and fundicgland polyps (See 7 WARNINGS AND PRECAUTIONS, Skin and Gastrointestinal).

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.

There have been post-market reports of microscopic colitis.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing system. Studies inhealthy 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 theabsorption 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 monitoredwhen such drugs are taken concomitantly with rabeprazole.

The impact of rabeprazole on different antiretroviral drugs is variable as shown in **Table 3**. Concomitant administration of rabeprazole may elevate and prolong serum levels of methotrexate and/or its metabolite. When used as combination therapy consisting of rabeprazole, amoxicillin and clarithromycin the resulting increased exposure to rabeprazole and 14-hydroxyclarithromycin is not considered clinically relevant.

9.4 Drug-Drug Interactions

The drugs listed in **Table 3** are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3: Established or Potential Drug-Drug Interactions

Class / Common Name	Source of Evidence	Effect	Clinical Comment
Antiretrovirals			
Rilpivirine	T	↓ rilpivirine exposure	Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect. See 2 CONTRAINDICATIONS.
Atazanavir	T	↓ Cmax and AUC of atazanavir	Co-administration of JAMP Rabeprazole with atazanavir is not recommended. Concomitant administration of omeprazole (20 mg or 40 mg QD substantially reduced plasma Cmax and AUC of atazanavir in healthy volunteers administered atazanavir or atazanavir/ritonavir See REYATAZ Product Monograph
Nelfinavir	C	↓ C_{max} and AUC of nelfinavir	Co-administration of JAMP Rabeprazole with nelfinavir is not recommended. Concomitant administration of

			omeprazole (40 mg QD) with nelfinavir (1250 mg BID) markedly reduced the AUC and Cmax for nelfinavir (by 36% and 37%, respectively) and its active metabolite M8 (by 92% and 89%, respectively) (see VIRACEPT Product Monograph)
Saquinavir	T	↑ saquinavir exposure	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. Concomitant administration of omeprazole (40 mg QD) with saquinavir/ritonavir (1000/100 mg BID) increased saquinavir AUC by 82% and Cmax by 75%. See INVIRASE Product Monograph.
Warfarin	CS	↑ INR and PTT	There have been reports of increased INR and PTT in patients receiving PPIs, including rabeprazole and warfarin concomitantly. Increases in INR and PTT may lead to abnormal bleeding and even death.
Cyclosporine	T	↑ cyclosporine	In vitro incubations employing human liver microsomes indicated that the degree of inhibition of cyclosporine metabolism by rabeprazole and omeprazole is similar at equivalent concentrations.
Methotrexate	CS	↑ methotrexate	Concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. No formal drug interaction studies of methotrexate with PPIs have been conducted.
Digoxin	CT	↑ digoxin plasma levels	Patients may need to be monitored when digoxin is taken concomitantly with rabeprazole.
Drugs dependent on gastric pH for absorption	CT	↓ ketoconazole	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. Therefore, patients may need to be Monitored when such drugs are taken concomitantly with rabeprazole.
Combination therapy with clarythromicin and amoxicillin	CT	↑ rabeprazole ↑ hydroxyclarithromycin	Combination therapy consisting of rabeprazole, amoxicillin and clarithromycin resulted in increases in plasma levels of rabeprazole and 14-hydroxyclarithromycin. See 10.3 Pharmacokinetics, Special Populations and Conditions, Combination Therapy with Antimicrobials. This increase in exposure to rabeprazole and the 14- hydroxyclarithromycin is not considered to be clinically significant.

Legend: CS = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

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

9.7 Drug-Laboratory Test 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, JAMP Rabeprazole treatment should be stopped 14 days before CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Rabeprazoleis an antisecretory compound (substituted benzimidazoleproton 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 has been characterized as a gastric proton pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion and produces dose- related sustained inhibition of both basal and stimulated gastric acid secretion.

10.2 Pharmacodynamics

Antisecretory Activity

The antisecretory effect begins within one hour after oral administration of rabeprazole (20 mg), and

reaches its maximum within two to four hours. The median inhibitory effect of rabeprazole on 24-hour gastric acidity is 88% of maximal after the first dose and the inhibition of acid secretion increases with repeated QD dosing to steady-state within seven days. Rabeprazole 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 4). 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 4: Gastric Acid Parameters – Rabeprazole versus Placebo After 7 Days of Once-Daily Dosing

Parameter	Rabeprazole (20 mg QD)	Placebo
Basal Acid Output(mmol/hr)	0.4[1]	2.8
Stimulated Acid Output (mmol/hr)	0.6[1]	13.3
% Time Gastric pH>3	65[1]	10

1. (p<0.01 versus placebo)

The ability of rabeprazole to cause a dose-related decrease in mean intragastric acidity is illustrated in Table 5.

Table 5: Mean AUC Acidity for Three Rabeprazole Doses versus Placebo

	Rabeprazole (mg QD)			
Parameter	10	20	40	Placebo
Mean AUC0-24 acidity (mmol·hr/L)	156[1]	131[1]	86[1]	678

1. p<0.001 versus placebo

The decrease in gastric acidity and the increase in gastric pH observed with 20 mg rabeprazole were compared to the same parameters with 20 mg omeprazole and placebo, asillustrated in Table 6.

Table 6: Gastric Acid Parameters – Rabeprazole versus Omeprazole and Placebo on Day 1 and Day 8 of Multiple QD Dosing

Parameter	Rabeprazole 20 mg QD		Omeprazole 20 mg QD		Placebo	
	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
Mean AUC0-24 Acidity	340.8[2,3]	176.9[2,4]	577.1[2]	271.2[2]	925.5	862.4
Median TroughpH (23-hr)[1]	3.77	3.51	1.43	3.21	1.27	1.38
% Time Gastric pH>3 [5]	54.6[2,3]	68.7[2,4]	36.7[2]	59.4[2]	19.1	21.7
% Time Gastric pH>4 [5]	44.1[2,3]	60.3[2,4]	24.7[2]	51.4[2]	7.6	11.0

1. No inferential statistics conducted for this parameter.
2. (p<0.001) versus placebo
3. (p<0.001) versus omeprazole 20 mg QD
4. (p<0.05) versus omeprazole 20 mg QD
5. 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 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 >4for at least 35% of the 24- hour period; this level was achieved in 90% of subjects receiving a 20 mg rabeprazole dose and in 100% of subjects receiving a 40 mg rabeprazole dose. With rabeprazole 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 for up to eight weeks to treat ulcerative orerosive 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 .

Effects on Enterochromaffin-like (ECL) Cells

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 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 (See 16 NON-CLINICAL TOXICOLOGY, Animal Pharmacology, Effects on Enterochromaffin-like (ECL) Cells).

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 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, luteotropic hormone, prolactin, somatotrophic hormone, dehydroepiandrosterone, cortisol-bind ing globulin, urinary 6 β-hydroxycortisol, and testosterone.

Other Effects

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

***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 24-hour intragastric acidity and plasma gastrin concentration were then assessed. Presented in Table 7 below are the placebo and rabeprazole data.

Table 7: 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[1] % Time pH>4	84.96	64.09	12.90	5.62
Mean[1] % Time pH>3	91.89	77.42	23.24	18.72
AUC[2] over 24 hrs	26.91	105.45	604.34	694.14

[1] Mean is the adjusted mean from ANOVA
[2] Values are means in mmol.h/L

10.3 Pharmacokinetics

Absorption:

JAMP Rabeprazole tablets are enteric-coated. Following oral administration, rabeprazole is rapidly absorbed and can be detected in plasma as early as 0.5 hours. 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%.

The rabeprazole C_{max} and AUC are linear with doses from 10 mg to 40 mg. Taking rabeprazole sodium delayed release 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.

The plasma half-life of rabeprazole is approximately one hour.

Distribution:

Rabeprazole is 96.3% bound to human plasma proteins. Rabeprazole does not accumulate and its pharmacokinetics are not altered by multiple dosing.

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.

Elimination:

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 in adolescents and children underthe age of 18 years has not been studied.

- **Geriatrics:**

In 20 healthy elderly subjects given a 20 mg rabeprazole dose QD for seven days, the AUC doubled and the C_{max} increased by 60% compared to measurements in a parallelyounger control group. There was no evidence of drug accumulation (see 7.1.4 Geriatrics).

- **Ethnic Origin:**

Rabeprazole is metabolized in the liver by cytochromes P450 3A (CYP3A) to a sulphone metabolite, and by 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.

- **Hepatic Insufficiency:**

In two studies in which 23 patients with varying degrees of chronic compensated hepatic cirrhosis were given a 20 mg rabeprazole 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 (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 BID 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 14-hydroxyclarithromycin 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 BID administration on days 2 to 6. As illustrated in Table 8, in the EM and PM subjects, an interaction was observed for clarithromycin, 14-hydroxyclarithromycin, 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}, was observed in the combination treatment when compared to monotherapy in EM subjects.

Table 8: Percent (%) Increase in Pharmacokinetic Parameters (C_{max} and AUC_{0-12}) for Extensive Metabolizers (EM) and Poor Metabolizers (PM) During Combination Therapy[1] vs. Monotherapy[2]

PHARMACOKINETIC Parameter		Active Substance			
		rabeprazole	clarithromycin	Clarithromycin M-5 metabolite (14-hydroxyclarithromycin)	Amoxicillin
% Increase C_{max} (µg/mL)	EM[3]	38%	11%	45%	11%
	PM[3]	22%	24%	67%	no interaction
% Increase AUC_{0-12} (µg·h/mL)	EM	32%	11%	46%	no interaction
	PM	35%	24%	73%	no interaction

1. Test treatment (combination therapy) consisted of clarithromycin 400 mg + amoxicillin 750 mg + rabeprazole 20 mg
2. Reference treatments (monotherapy) : A: clarithromycin 400 mg; B: amoxicillin 750 mg; C: rabeprazole 20 mg
3. EM = Extensive Metabolizer; PM = Poor Metabolizer

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-25°C) protected from moisture and high temperature.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

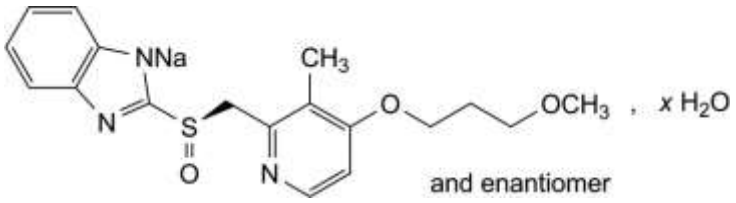
Drug Substance

Proper name: Rabeprazole Sodium Hydrate

Chemical name: Sodium 2-[(RS)-[[4-(3-Methoxypropoxy)-3-methylpyridin-2-yl] methyl]sulfinyl] benzimidazol-1-idehydrate

Molecular formula and molecular mass: $C_{18}H_2ON_3NaO_3S$, x H_2O, 381.4 g/mol (anhydrous substance)

Structural formula:



Physicochemical properties: Rabeprazole sodium hydrate is a white to slightly yellowish- white hygroscopic, amorphous or crystalline powder. It is very soluble to freely soluble in water, freely soluble in anhydrous ethanol, practically insoluble in heptane.

14. CLINICAL TRIALS

14.1 Clinical Trials by Indication

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

Trial Design and Study Demographics

The healing of erosive or ulcerative GERD was studied in 3 clinical trials.

Study 1

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 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.

Study 2

In a U.S. multicentre, double-blind, active-controlled study of 338 patients, 20 mg rabeprazole QD was compared to Ranitidine 150 mg four times daily (QID).

Study 3

In an international, double-blind, active-controlled study of 202 patients were treated with a 20 mg rabeprazole dose QD or 20 mg omeprazole QD for up to eight weeks.

Study Results

Study 1

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 dosing and placebo are presented in Table 9.

Table 9: Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease(GERD) – Percentage of Patients Healed

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

* p<0.001 vs. placebo

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

Study 2

Rabeprazole was statistically superior to ranitidine with respect to the percentage of patients healed at endoscopy after four and eight weeks of treatment (see Table 10).

Table 10: Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease(GERD) – Percentage of Patients Healed

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

Study 3

Rabeprazole was comparable to omeprazole in producing endoscopic healing. The percentage of

patients healed at endoscopy at four and eight weeks are given in Table 11.

Table 11: Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease(GERD) – Percentage of Patients Healed

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

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

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

Trial Design and Study Demographics

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 dose QD or placebo.

Study Results

In both studies, rabeprazole was significantly superior to placebo in the maintenance of GERD healing. Table 12 gives results from a combined analysis of the two studies for the percentages of patients with endoscopically maintained healing.

Table 12: Long-term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERDMaintenance) – Percentage of Patients in Endoscopic Remission

Week	Rabeprazole 10 mg QD	Rabeprazole 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 10 mg QD

In both multicentre trials rabeprazole 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 night time ($p\leq0.003$) heartburn severity.

Symptomatic Gastroesophageal Reflux Disease (GERD)

Trial Design and Study Demographics

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, ata 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.

Study Results

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 mg 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 13 and 14 below.

Table 13: Complete Relief of Heartburn and Satisfactory Relief of Heartburn Frequency from Study RAB-USA-2

	PLACEBO n (%)†	Rabeprazole 10 mg QDn (%)†	Rabeprazole 20 mg QDn (%)†
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 14: Complete Relief of Heartburn and Satisfactory Relief of Heartburn Frequency from Study RAB-USA-3

	PLACEBO n (%)†	Rabeprazole 20 mg QDn (%)†
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

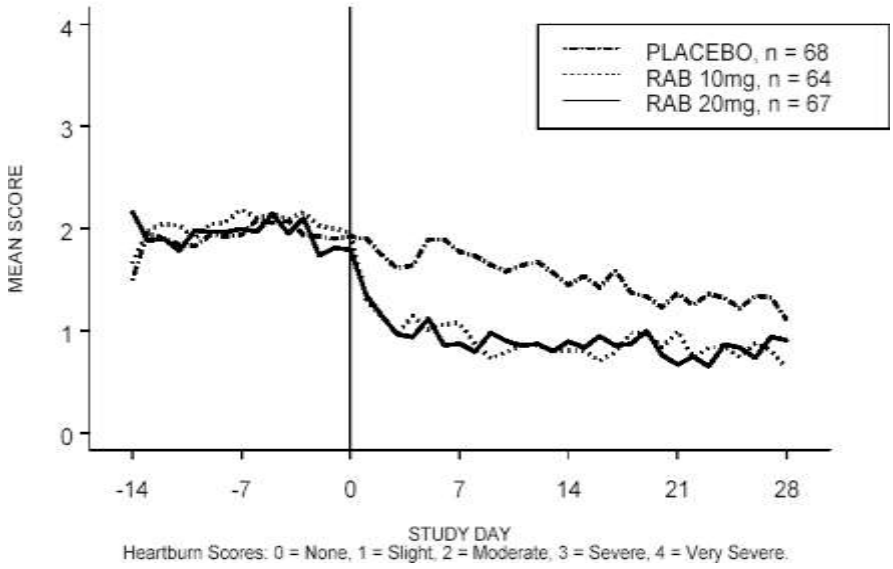
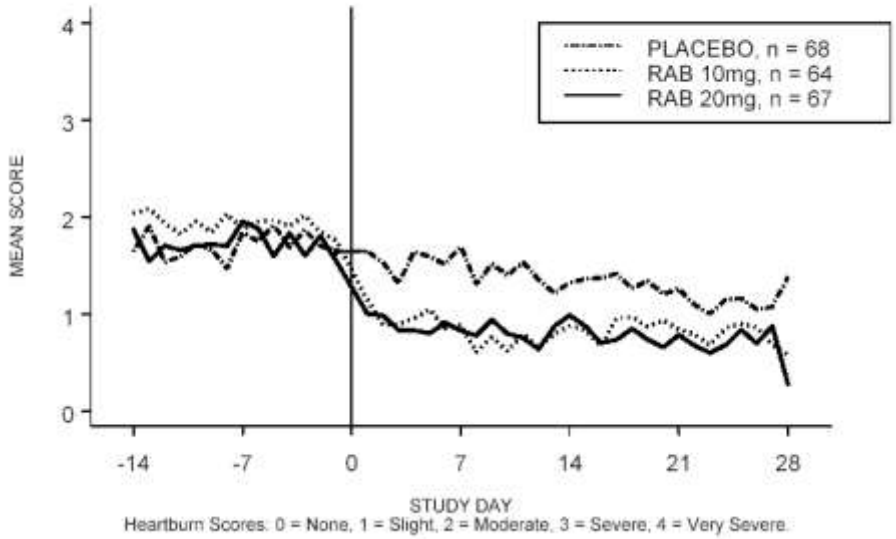
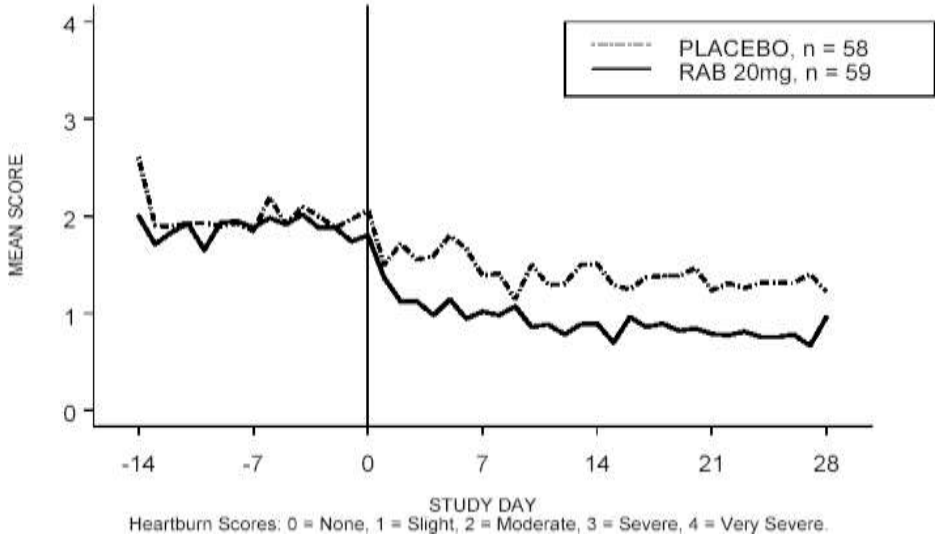


Figure 2: Mean Nighttime heartburn scores RAB - USA - 2



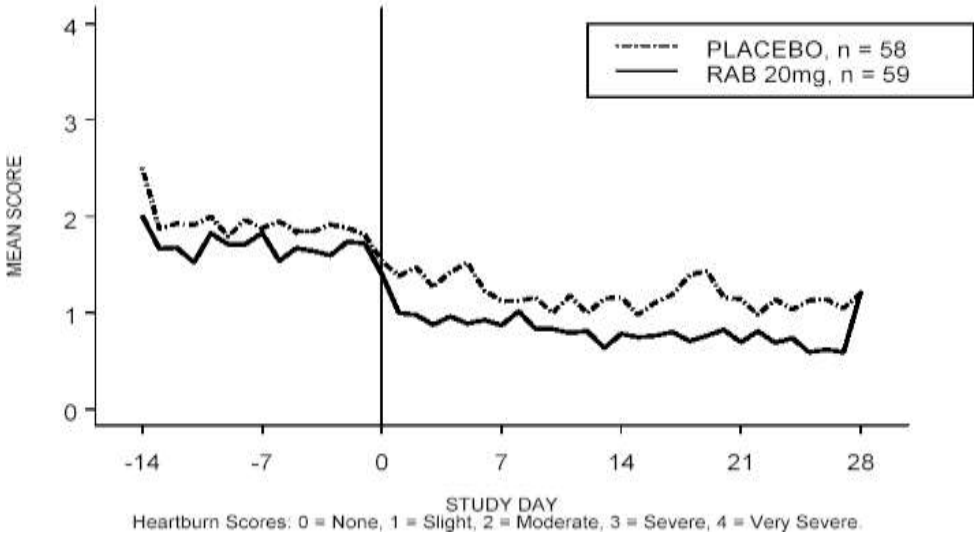
Heartburn Scores: 0 = None, 1 = Slight, 2 = Moderate, 3 = Severe, 4 = Very Severe.

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



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

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



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

Healing of Duodenal Ulcers

Trial Design and Study Demographics

Placebo Controlled Study

In a U.S. double-blind, multicentre study assessing the effectiveness of 20 mg and 40 mg rabeprazole dosages QD versus placebo for healing endoscopically defined duodenal ulcers, 100 patients were treated for up to four weeks.

Active Controlled Study

In a U.S. multicentre, double-blind, active-controlled trial, 376 patients with endoscopically defined duodenal ulcers were treated with a 20 mg rabeprazole dose QD or ranitidine 150 mg BID for up to four weeks.

PPI Controlled Study

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

Study Results

Placebo Controlled Study
Rabeprazole was significantly superior to placeboin producing healing of duodenal ulcers. The percentages of patients with endoscopic healing are presented in Table 15.

Table 15: Healing of Duodenal Ulcers – Percentage of Patients Healed

Week	Rabeprazole 20 mg QD	Placebo
	N=34	N=33

2	44%	21%
4	79%[1]	39%

1. p=0.001 vs. placebo

Patients treated with a rabeprazole 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 20 mg QD was significantly more effective than placebo in reducing daily antacid use (p<0.001).

Active Controlled Study

The percentages of patients with endoscopic healing in the active controlled study at two and four weeks are presented in Table 16.

Table 16: Healing of Duodenal Ulcers – Percentage of Patients Healed

Week	Rabeprazole 20 mg QD	Ranitidine 150 mg BID
	N=188	N=188
2	40%[1]	26%
4	83%[2]	73%

1. p=0.002 vs. ranitidine
2. p=0.017 vs. ranitidine

Additionally, rabeprazole 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 night time ulcer pain severity (week 2, p=0.044), and in reducing antacid consumption (p=0.037).

PPI Controlled Study

In the PPI controlled study ,the percentages of patients with endoscopic healing at two and four weeks are presented in Table 17.

Table 17: Healing of Duodenal Ulcers – Percentage of Patients Healed

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

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

Healing of Gastric Ulcers

Trial Design and Study Demographics

Placebo Controlled Study

In a U.S. double-blind, multicentre study assessing the effectiveness of a 20 mg and 40 mg rabeprazole dosage QD versus placebo for healing endoscopically defined gastric ulcers, 94 patients were treated for up to six weeks.

Active Controlled Studies

In two active-controlled trials of rabeprazole, one conducted in the U.S. versus ranitidine 150 mg BID and one conducted in Europe versus omeprazole 20 mg compared the rates of endoscopic healing of gastric ulcers.
In another European study, rabeprazole 20 mg dose QD to omeprazole 20 mg.

Study Results

Placebo Controlled Study

Rabeprazole was significantly superior to placebo in producing healing of gastric ulcers. The percentages of patients with endoscopic healing at three andsix weeks are presented in Table 18.

Table 18: Healing of Gastric Ulcers – Percentage of Patients Healed

Week	Rabeprazole 20 mg QD	Placebo
	N=32	N=31
3	32%	29%
6	90%[1]	39%

1. p<0.001 vs. placebo

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

Active Controlled Studies

In two active-controlled trials of rabeprazole , 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 20 mg dose QD to omeprazole 20 mg, rabeprazole 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).

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

Trial Design and Study Demographics
Twelve patients with idiopathic gastric hypersecretion or Zollinger-Ellison syndrome have been treated successfully with rabeprazole doses from 20 to 120 mg for up to 12 months.

Study Results
Rabeprazole treatment produced satisfactory inhibition of gastric acid secretion in all patients and complete resolution of signs and symptoms of acid-peptic disease where present.

Rabeprazole treatment also prevented recurrence of gastric hypersecretion and manifestation s of acid-peptic disease in all patients. The high doses of rabeprazole used to treat this small cohort of patients with gastric hypersecretion were not associated with drug-related adverse effects.

H. pylori Eradication

Trial Design and Study Demographics

Study 604

The U. S. multicentre double-blind, parallel-group compared rabeprazole, amoxicillin, and clarithromycin for 3, 7, or 10 days vs. omeprazole, amoxicillin and clarithromycin for10 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 BID (RAC) or omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg, all BID (OAC).

Study 603

The European multicentre study 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 BID, or omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1000 mg, all BID.

Study Results

Results for Study 604 and Study 603 are presented below in Table 19.

Table 19: *H. pylori* eradication[1] 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[2]	Intent-to-Treat[3]
Study 604 North America	Rabeprazole	3 days	30% [-61%, -43%] (n=167)	27% [-55%, -37%] (n=187)
	Rabeprazole	7 days	84%4 [-5%, +11%] (n=166)	77%4 [-4%, +12%] (n=194)
	Rabeprazole	10 days	86%4 [-3%, +12%] (n=171)	78%4 [-4%, +13%] (n=196)
	Omeprazole	10 days	82% (n=179)	73% (n=206)
Study 603	Rabeprazole	7 days	94% [-0.7%,	84% [+0.5%,

Europe			+20%] (n=65)	+24.5%] (n=83)
	Omeprazole	7 days	84% (n=63)	72% (n=85)

1. In Study 604, H. pylori eradication was assessed at 6 w eeks but not more than 10 weeks by 13C-UBT. In Study 603, successful eradication of H. pylori was defined as a negative 13C-UBT at week 5 and week 13 post-treatment assessments.
2. Patients were included in the analysis if they had H. pylori infection documented at baseline, defined as a positive 13C-UBT plus rapid urease test or culture and were not protocol violators. Patients who dropped out of the study due to an adverse event related to the study drug were included in the evaluable analysis as failures of therapy.
3. Patients were included in the analysis if they had documented H. pylori infection at baseline defined as a positive 13C-UBT plus rapid urease test or culture, and took at least one dose of study medication.
4. Equivalent to OAC; two-sided 95% confidence interval on the difference between regimens is within [-15%,+15%].

Study 604

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 19 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 20 Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes.).

Study 603

In Study 603, successful eradication of *H. pylori* was defined as a negative ^{13}C-UBT at both the Week 5 and Week13 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 20).

14.2 Comparative Bioavailability Studies

14.2 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of JAMP-Rabeprazole 20 mg tablets (JAMP Pharma Corporation) and ^{Pr}PARIET® 20 mg tablets (Janssen-Ortho Inc.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from 49 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Rabeprazole (1 x 20 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	841.5 984.0 (59.2)	809.5 982.0 (64.3)	103.9	91.8 – 117.6
AUC_I (ng·h/mL)	853.3 996.7 (59.3)	841.3 1006.2 (62.9)	101.3	91.6 – 112.2
C_{max} (ng/mL)	405.3 473.7 (50.5)	395.2 500.8 (58.6)	102.7	81.6 – 129.3
T_{max}[3] (h)	4.0 (2.0 – 9.0)	3.3 (2.0 – 9.0)		
$T_{½}$[4] (h)	2.3 (82.3)	3.0 (152.1)		

[1] JAMP-Rabeprazole (rabeprazole sodium) delayed-release tablets, 20 mg (JAMP Pharma Corporation)
[2] PrPARIET® (rabeprazole sodium) enteric-coated tablets, 20 mg (Janssen-Ortho, Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

A randomized, two-way, single-dose, crossover comparative bioavailability study of JAMP-Rabeprazole 20 mg tablets (JAMP Pharma Corporation) and PrPARIET® 20 mg tablets (Janssen-Ortho Inc.) was conducted in healthy, adult, male subjects under high-fat, high-calorie fed conditions. Comparative bioavailability data from 54 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Rabeprazole (1 x 20 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	1235.1 1412.0 (48.9)	1220.6 1370.0 (48.0)	101.2	94.2 – 108.6
AUC_I (ng·h/mL)	1273.4 1442.8 (47.8)[3]	1230.5 1380.8 (48.1)	102.5	95.8 – 109.7
C_{max} (ng/mL)	723.1 801.3 (38.5)	698.6 773.7 (36.5)	103.5	90.5 – 118.4
T_{max}[4] (h)	6.3 (2.0 – 24.0)	6.3 (2.0 – 24.0)		
$T_{½}$[5] (h)	2.1 (61.3)[3]	2.4 (160.2)		

[1] JAMP-Rabeprazole (rabeprazole sodium) delayed-release tablets, 20 mg (JAMP Pharma Corporation)
[2] PrPARIET® (rabeprazole sodium) enteric-coated tablets, 20 mg (Janssen-Ortho, Inc.)
[3] n=53
[4] Expressed as the median (range) only
[5] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

Rabeprazole sodium, amoxicillin and clarithromycin triple therapy has been shown to be active against most strains of *H. pylori in vitro* and in clinical infections. **See 14.1 Clinical Trials by Indication, Eradication of *H. Pylori*.**

Helicobacter pylori

Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin usingagar 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 0.5µg/ 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 20 below.

Table 20: Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes[1] for Triple Therapy- Intent to Treat

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

1 Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results.
2 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-resistantat baseline; in one case the *H. pylori* was eradicated. In the 7- and 10-day treatment groups, respectively, 75% (107/145) and 79% (112/142) of the patients who had pretreatment amoxicillin- susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H.* pylori. No patients developed amoxicillin- resistant *H. pylori* during therapy.

Rabeprazole activity against *H. pylori*

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

16 NON-CLINICAL TOXICOLOGY

General 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 21).

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 21: List of Acute (Single-Dose) Toxicity Studies

Species/ Strain (Status)	Number/ Gender/ Group	Route ofAdmin./ Vehicle	Dose	Duration	LD_{50} or NOEL	
					M	F
Mouse/ICR (Oral route: fasted 19 - 22 hrs prior to dosing; i. v. route: *ad libitum* feeding	5 per sex per group	p.o. (gavage)/ purified water	Male: 629, 786, 983, 1229, 1536, 1920, and 2400 mg/kg Female: 629, 786, 983, 1229, 1536, 1920, 2400 and 3000 mg/kg	Single dose	1206	1012
		i.v./ physiological saline	Male: 131, 164, 205, 256, and 320 mg/kg Female: 164, 205, 229, 256, and 320 mg/kg		220	237
Rat/Slc: SD (oral route: fasted 17 - 24 hrs prior to dosing; i.v. route: *ad libitum* feeding)	5 per sex per group	p.o. (gavage)/ purified water	Male: 819, 1024, 1280, 1431, 1600, and 2000 mg/kg Female: 655, 819, 1024, 1280, 1600, and 2000 mg/kg	Single dose	1447	1322
		i.v./ physiological saline	Male: 98, 123, 154, 172, and 192 mg/kg Female: 98, 123, 154, 192, 240, and 300 mg/kg		157	152
Rat Slc:SD (*ad libitum* feeding)	5 per sex per group	i.v./NaOH and physiologicalsaline	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 fastedover night)	5 per sex per group	Degradation Products I and IIand Impurity p. o. (gavage) Metabolite i.v./0.5 methylcellulose solution	Degradation Prod. I : 0, 500, and 1500 mg/kg Degradation Prod. II: 50, 150, and 500 mg/kg Impurity: 500 and 1500 mg/kgMetabolite: 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	p.o (gavage)/ purified water	80, 400, and 2000 mg/kg	Single dose	> 2000	> 2000

* Rabeprazole sodium

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.

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 infemales 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 andliver weight was increased.

Dog

Rabeprazole sodium had no effect on liver, kidney, heart, or lung at doses up to and including30 mg/kg given by oral administration. Because of the smaller thymus weights observed infemales 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 andno 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 andemesis 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 NOEL or 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. 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 onthe gastric mucosa were not observed at 0.2 mg/kg in a 52-week dog study. A four-week study in antrectromized 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 anddogs. 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

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 exceed 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.

Carcinogenicity:
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 therecommended 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 abody 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 upto 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-cresidinedaily 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 testingfacility historical control data, or from data published in literature (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.

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

The CHO/HGPRT Forward Gene Mutation Assay

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

Ames Tests

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

The L5178Y TK Mouse Lymphoma Assay

Rabeprazole was negative for inducing mutations in L5178Y TK+/- cells when testing in the absence of metabolic activation, but was weakly positive when tested at concentrations of 25 and 30 µg/mL in the presence of metabolic activation.

Reproductive and Developmental Toxicology:

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. Rabeprazole does not cause Leydig cell tumours or perturbations of the LH/T axis.

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 22, below.

Table 22: 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

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.

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.

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 23.

Table 23: 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.

Rabeprazole sodium had no inhibitory effect on lesion healing or collagen regeneration in ethanol-HCl-induced ulcers in rats; whereas, histamine H2-receptor antagonists (cimetidine and famotidine) had inhibitory effects on lesion healing and collagen synthesis

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/m2) basis in patients given the recommended 20 mg/day (12.3 mg/m2) 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

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 effecton biliary or pancreatic secretion in anesthetized rats.

Pharmacokinetics – Non-clinical Studies

Absorption and Pharmacokinetics

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

Stereochemical Pharmacokinetic Considerations

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

In the rat, co-administration of both enantiomers of rabeprazole sodium as the RS (") racemate (40 mg/kg, i.v.) produced pharmacokinetic results comparable to those when R(+)-rabeprazole sodium and S(-)-rabeprazole sodium were administered separately (20 mg/kg, i.v.). The R/S ratios for AUC value, total clearance, and volume of distribution were 1.34, 0.67, and 0.62 respectively. 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 theindividual 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 smallerextent 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 fallento <0.2 µg-equiv/g by Day 28. In another study, tissue distribution was similar after p.o. and i.v. administration, and radioactivity in excess of that in plasma persisted in thyroid, choroid, and to a lesser extent, in lens and retina 8 days post-dose. Radioactivity in gastric mucosa 0.5 hours after i.v. administration was two times higher than in plasma. Pretreatment with pentagastrin resulted in higherlevels 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 i.v. 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PARIET® (rabeprazole sodium enteric-coated tablets, 10 mg and 20 mg), submission control 261225 , Product Monograph, Janssen Inc. Canada, AUG 08, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]JAMP Rabeprazole
(Rabeprazole Sodium Delayed Release Tablets)

Read this carefully before you start taking **JAMP 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 **JAMP Rabeprazole**.

What is JAMP Rabeprazole used for?
JAMP Rabeprazole is used in adults to treat conditions where reducing stomach acid production is needed, such as:

- 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-Ellisonsyndrome).
- treat ulcers caused by infection with the bacterium, Helicobacter pylori (H. pylori), and preventthese ulcers from coming back by:
  - taking JAMP Rabeprazole with antibiotics such as amoxicillin and clarithromycin, asdirected by your doctor.
  - following the information on the antibiotics provided to you by the pharmacist.

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

What are the ingredients in JAMP Rabeprazole?
Medicinal ingredients: rabeprazole sodium (as rabeprazole sodium hydrate).

Non-medicinal ingredients: Diethyl Phthalate, Ethyl Cellulose (7 cps), Ferric Oxide Red,Ferric Oxide Yellow, Hypromellose Phthalate, Mannitol, Magnesium Oxide, Magnesium Stearate, Povidone, Sodium Starch Glycolate, Talc, Titanium Dioxide and black ink (shellac glaze, iron oxide black and propylene glycol).

JAMP Rabeprazole comes in the following dosage forms:
Tablets of 10 mg and 20 mg

Do not use JAMP Rabeprazole if:

- you are allergic to:
  - rabeprazole or other medications in this class.

- the "non medicinal" ingredients in JAMP Rabeprazole tablets (see **What are the ingredients in JAMP Rabeprazole?**).
- you are taking rilpivirine
- you are unable to take amoxicillin or clarithromycin if you are using JAMP Rabeprazole to treatulcers caused by an infection (*H. pylori*)

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

- have any liver problems
- 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
- are taking methotrexate
- are pregnant or planning to become pregnant
- are breast-feeding or planning to breast-feed
- are due to have a specific blood test (Chromogranin A)

Other warnings you should know about:
Long-term use of JAMP 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 JAMP 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 JAMP 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 JAMP Rabeprazole.

Tell your healthcare professional about all the medicines you take, including any drugs vitamins, minerals, natural supplements or alternative medicines.

The following may interact with JAMP Rabeprazole:
- ketoconazole
- digoxin
- warfarin
- antiretroviral drugs such as atazanavir, nelfinavir, saquinavir
- methotrexate

How to take JAMP Rabeprazole:
- Take JAMP Rabeprazole exactly as prescribed by your doctor, usually for a specific number ofweeks.
- Use the lowest dose and shortest time as determined by your doctor.
- Do not stop taking JAMP Rabeprazole even when you start to feel better. If you stop takingJAMP Rabeprazole too soon, your symptoms may return.
- Take JAMP 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[1]	20 mg	twice daily in combination with antibiotic drugs (500 mg clarithromycin and 1000 mg amoxicillin) preferably with the morning and evening meals	one week

1. If you are given JAMP 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, or a person you are caring for, have taken too much JAMP Rabeprazole, contact a 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 JAMP 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 regularschedule**.

What are possible side effects from using JAMP Rabeprazole?

Like all medicines, JAMP Rabeprazole can cause side effects.

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

If you experience symptoms of low magnesium levels in your body, your doctor may stop JAMP 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.
- fracture (broken bone).
- 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.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Subacute cutaneous lupus erythematosus (SCLE). New or worsening joint pain and rash that gets worse in the sun		✓	
Severe diarrhea accompanied with blood and/or mucous			✓
Clostridium difficile colitis (Bowel inflammation): Symptoms include severe (watery or bloody) diarrhea, fever, abdominal pain or tenderness			✓
Clostridium difficile colitis (Bowel inflammation): If you are currently taking or have recently taken antibiotics and you develop diarrhea, contact your doctor, even if the diarrhea is relatively mild.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Microscopic colitis (inflammation of the gut): • Chronic watery diarrhea • Abdominal pain, cramps or bloating • Weight loss • Nausea • Uncontrollable bowel movement • Signs of Dehydration such as Extreme thirst, Less frequent urination, Dark-coloured urine, Fatigue, Dizziness, Confusion The symptoms of microscopic colitis can come and go frequently. If you have watery diarrhea that lasts more than a few days, contact your doctor.	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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:
Keep your tablets stored at room temperature (15-25°C) and protect from moisture and high temperature.

Keep out of the sight and reach of children.

If you want more information about JAMP Rabeprazole:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug- product-database.html); the manufacturer's website www.jamppharma.com, or by calling 1- 866-399-9091.

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