

PARIET[®] Tablets

PRODUCT INFORMATION

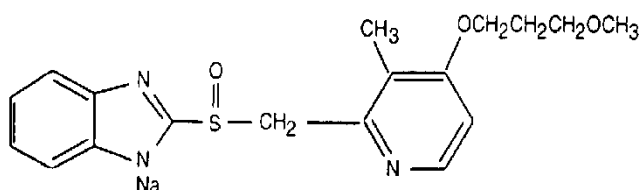
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red CI 77491 and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow CI 77492 and Edible Ink Red A1.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric PARIETal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ mL/min/1.73 m}^2$), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $\text{AUC}_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

Clinical trials

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD

Percentage of Patients Healed		
Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD): The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD
Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers: In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p = 0.001$) after four weeks treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

**Table 3. Duodenal Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers: PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

**Table 4 Gastric Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

H. pylori eradication: In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxycillin 1g twice daily for a total of 7 days ($n = 83$), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxycillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 hypomagnesia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and then periodically while treatment continues (see **ADVERSE REACTIONS**).

***Fractures**

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

***Concomitant use of Rabeprazole with Methotrexate**

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

***Clostridium difficile**

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as Clostridium difficile.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interactions with Other Drugs

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Patients may need to be monitored when these drugs are taken together with PARIET.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxycillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

Nervous System: headache, dizziness.

Gastrointestinal: diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.

Respiratory: rhinitis, pharyngitis, cough.
Musculoskeletal: non-specific pain, back pain, myalgia.
Skin: rash.
Other: asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

Gastrointestinal: dyspepsia, eructation, dry mouth.
Respiratory: sinusitis, bronchitis.
Musculoskeletal: arthralgia, leg cramps.
Urinary: urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema. Rare ($\geq 0.01\%$ and $< 0.1\%$)

Gastrointestinal: anorexia, gastritis, weight gain, stomatitis.
Skin: pruritis, sweating.
Special Senses: vision or taste disturbances.
Haematologic: leucocytosis.
Other: depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome.

There have been post-marketing reports of bone fractures (see **PRECAUTIONS).*

DOSAGE AND ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **PRECAUTIONS**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

Eradication of H. pylori: Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal or hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION

PARIET 10 mg are pink, biconvex tablets, marked with “ε 241” in black ink on one side. Supplied in blister packs of 28 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with “ε 243” in red ink on one side. Supplied in blisters pack of 5 and 30 tablets.

Storage

PARIET tablets should be stored below 25°C. Do not refrigerate or freeze.

Tablets are presented in an aluminium/aluminium blister.

SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

Date of first inclusion in the ARTG: 31 October 2000

Date of most recent amendment: 14 June 2013

*Please note changes (presented as **italicised text*) in Product Information.

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PARIET[®] Tablets

PRODUCT INFORMATION

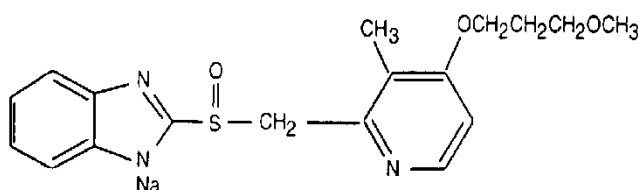
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red CI 77491 and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow CI 77492 and Edible Ink Red A1.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric PARIETal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ mL/min/1.73 m}^2$), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $\text{AUC}_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

Clinical trials

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD

Percentage of Patients Healed		
Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD): The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD
Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers: In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p = 0.001$) after four weeks treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

**Table 3. Duodenal Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers: PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

**Table 4 Gastric Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

H. pylori eradication: In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxycillin 1g twice daily for a total of 7 days ($n = 83$), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxycillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

***Fractures**

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

***Concomitant use of Rabeprazole with Methotrexate**

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

***Clostridium difficile**

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as Clostridium difficile.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interactions with Other Drugs

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

**Clopidogrel:* Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Patients may need to be monitored when these drugs are taken together with PARIET.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema. **Rare ($\geq 0.01\%$ and $< 0.1\%$)**

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome.

There have been post-marketing reports of bone fractures (see **PRECAUTIONS).*

DOSAGE AND ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **PRECAUTIONS**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal or hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION

PARIET 10 mg are pink, biconvex tablets, marked with "ε 241" in black ink on one side. Supplied in blister packs of 28 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with "ε 243" in red ink on one side. Supplied in blisters pack of 5 and 30 tablets.

Storage

PARIET tablets should be stored below 25°C. Do not refrigerate or freeze.

Tablets are presented in an aluminium/aluminium blister.

SPONSOR

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Date of most recent amendment: 26 July 2013

*Please note changes (presented as **italicised text*) in Product Information.

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PARIET[®] Tablets

PRODUCT INFORMATION

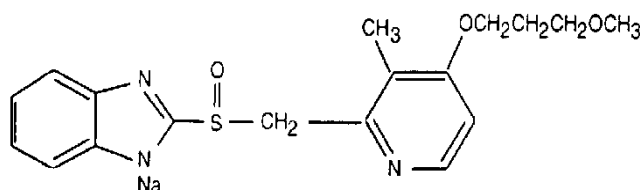
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red CI 77491 and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow CI 77492 and Edible Ink Red A1.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric PARIETal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ mL/min/1.73 m}^2$), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $\text{AUC}_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

Clinical trials

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD

Percentage of Patients Healed		
Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD): The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD
Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers: In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p = 0.001$) after four weeks treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

**Table 3. Duodenal Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers: PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

**Table 4 Gastric Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

H. pylori eradication: In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxycillin 1g twice daily for a total of 7 days ($n = 83$), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxycillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ^{14}C -labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m^2) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Patients may need to be monitored when these drugs are taken together with PARIET.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxycillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema. Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including

thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome.

There have been post-marketing reports of bone fractures (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **PRECAUTIONS**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxycillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal or hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET 10 mg are pink, biconvex tablets, marked with “ε 241” in black ink on one side. Supplied in blister packs of 28 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with “ε 243” in red ink on one side. Supplied in blisters pack of 5 and 30 tablets.

Storage Conditions

PARIET tablets should be stored below 25°C. Do not refrigerate or freeze.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG:

31 October 2000

DATE OF MOST RECENT AMENDMENT:

24 April 2015

® PARIET is a trademark of Eisai Ltd.

PARIET[®] Tablets

Rabeprazole sodium

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about PARIET tablets. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking PARIET against the benefits this medicine is expected to have for you.

If you have any concerns about using PARIET ask your doctor or pharmacist.

Keep this leaflet with your medicine.

You may need to read it again.

What PARIET is used for

The name of your medicine is PARIET. It contains the active ingredient rabeprazole sodium.

PARIET belongs to a group of medicines called proton pump inhibitors (PPIs). PARIET works by decreasing the amount of acid the stomach makes, to give relief from the symptoms and allow healing to take place. Your food will still be digested in the same way.

Gastro-oesophageal reflux disease:

PARIET is used to treat gastro-oesophageal reflux disease (GORD), commonly known as 'reflux'. This can be caused by food and acid from the stomach flowing the wrong way

(reflux) back up the food pipe, also known as the oesophagus.

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn. PARIET is also used to help stop gastro-oesophageal reflux disease from coming back or relapsing.

Peptic Ulcers:

PARIET is used to treat peptic ulcers. Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum, which is the tube leading out of the stomach.

These ulcers can be caused by too much acid being made in the stomach.

Most people who have a peptic ulcer also have bacteria called *Helicobacter pylori* in their stomach. Your doctor may also prescribe a course of antibiotics (clarithromycin and amoxycillin) for you. When PARIET is taken with antibiotics, the combination therapy will kill the *Helicobacter pylori* and let your ulcer heal.

Chronic Gastritis:

The presence of the bacteria *Helicobacter pylori* may cause the stomach to become inflamed, resulting in pain, nausea and vomiting; all of which are signs of chronic gastritis.

When PARIET tablets are taken with antibiotics, they will help kill *Helicobacter pylori* and allow the stomach to heal.

Your doctor may have prescribed PARIET for another reason. Ask

your doctor if you have any questions about why PARIET has been prescribed for you.

PARIET is only available with a doctor's prescription.

Before you take PARIET

When you must not take it:

Do not take PARIET if you have an allergy (hypersensitivity) to:

- rabeprazole sodium
- any of the ingredients listed at the end of this leaflet.
- other proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole).

Symptoms of an allergic (hypersensitive) reaction may include:

- rash, itching or hives on the skin
- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body

Do not take PARIET if:

- the packaging is torn or shows signs of tampering.
- the expiry date (month and year) printed on the pack has passed. If you take PARIET after the expiry date it may not work.

PARIET should not be given to children under 18 years of age. Safety and effectiveness of PARIET in children has not been established.

Before you start to take it:**You must tell your doctor if:**

- you are pregnant or intend to become pregnant.
- you are breast-feeding or intend to breast-feed. It is not known if PARIET passes into breast milk.
- you have now, or have had in the past, liver problems.

Taking other medicines:

Tell your doctor or pharmacist if you are taking any other medicines, including medicines you can buy without a prescription from a pharmacy, supermarket or health food shop.

Do not take PARIET and tell your doctor or pharmacist if you are taking any of the following:

- atazanavir, a medicine used (with other antiretrovirals) to treat HIV-1 infection.
- clopidogrel, an antiplatelet medicine.

You should not take PARIET while taking these medicines.

Also tell your doctor or pharmacist if you are taking any of the following:

- cyclosporin, a medicine used to treat several conditions including prevention of graft rejection following kidney, liver or heart transplantation; severe, active rheumatoid arthritis; severe skin diseases; kidney disease where other treatments have failed.
- methotrexate, a medicine used to treat some kinds of cancer. It is also used to treat psoriasis (skin disease) and rheumatoid arthritis.
- digoxin, a medicine used to treat heart problems.
- ketoconazole, a medicine used to treat fungal infections.
- mycophenolate mofetil, a medicine used to prevent organ rejection following kidney, liver or heart transplants.

- clarithromycin, a medicine used to treat infections.

These medicines may be affected by PARIET or may affect how well PARIET works. Your doctor or pharmacist can tell you what to do if you are taking any other medicines.

If you have not told your doctor or pharmacist about any of the above, tell them before you start taking PARIET.

Your doctor will advise you whether or not to take PARIET or if you need to have your dose adjusted.

How to take PARIET

Follow the directions given to you by your doctor and pharmacist carefully. They may differ from the information contained in this leaflet.

How much to take:**Adults**

The usual dose is one tablet, to be taken once daily, at the same time each day.

The dose of PARIET tablets is usually 20 mg, but may vary from 10 mg to 40 mg per day depending on what condition you are being treated for and how severe it is.

For treating *Helicobacter pylori* infections in combination with antibiotics (clarithromycin and amoxycillin), the usual dose is one 20mg tablet twice daily, morning and evening, for 7 days.

Children

PARIET should not be given to children under 18 years of age. Safety and effectiveness of PARIET in children has not been established.

How to take it:

- PARIET should be swallowed whole, with a glass of water or other liquid.
- Do NOT crush or chew the tablets. They have a special

coating, which protects them from the acid in your stomach. If the coating is broken by chewing, the tablets may not work.

- It does not matter if you take PARIET with food or on an empty stomach.

Ask your doctor or pharmacist for help if you do not understand the instructions provided with this medicine.

If you forget to take it:

If you forget to take your tablet, take it as soon as you remember and then continue to take it as you would normally.

However, if it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you are not sure what to do, check with your doctor or pharmacist.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you have taken too much (overdose):

If you think that you, or anyone else, may have taken too much PARIET, immediately telephone your doctor or the Poisons Information Centre (telephone 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

While you are using PARIET

Things you must do:

- Use PARIET exactly as your doctor has prescribed.
- Always swallow PARIET tablets whole.

- Tell your doctor if you become pregnant while you are taking PARIET

Tell your doctor or pharmacist that you are taking PARIET if you are about to start taking a new medicine.

Things you must not do:

- Do not use PARIET to treat any other complaint unless your doctor says to.
- Do not give this medicine to anyone else, even if they have the same symptoms as you.
- Do not crush or chew the tablets.
- Do not give PARIET to children.

Side Effects

PARIET is usually well tolerated but tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking PARIET.

PARIET helps most people with peptic ulcers or reflux disease, but it may have unwanted side effects in a few people.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some side effects.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor if you notice any of the following and they worry you:

- headache
- dizziness
- diarrhoea
- nausea
- stomach pain
- wind
- vomiting

- constipation
- runny or blocked nose
- sore throat and discomfort when swallowing
- cough
- pain (including back, chest or joint pain)
- muscle weakness, physical weakness or lack of energy
- rash or itchy rash accompanied by skin eruptions or blisters
- flu-like symptoms
- sleeplessness (insomnia)
- indigestion
- belching
- dry mouth
- leg cramps
- swelling of the arms or legs
- nervousness
- sleepiness (somnolence)
- loss of appetite for food (anorexia)
- weight gain
- sweating

These side effects are usually mild.

Tell your doctor immediately if you notice any of the following:

- painful and/or frequent urination (common symptoms of a urinary tract infection)
- vision or taste disturbance
- depression
- feeling dizzy, faint, lightheaded or weak (hypotension)
- shortness of breath
- signs of frequent infections such as fever, chills, sore throat or mouth ulcers.

These are serious side effects. You may need urgent medical attention. Serious side effects are rare.

Tell your doctor immediately and do not take your next dose of PARIET if you experience:

- signs of allergy such as skin rash, reddening, blisters or itching, swelling of the face, lips or other

parts of the body, shortness of breath or wheezing.

If you experience symptoms such as severe (watery or bloody) diarrhoea, fever, abdominal pain or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation).

Other problems are more likely to arise from the ulcer itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

Under rare circumstances supervised by the doctor, proton pump inhibitors (PPIs) might be used for long periods of time.

Low magnesium can occur in some people who take a proton pump inhibitor. Symptoms of low magnesium can include: seizures, dizziness, spasms, cramps or muscle weakness.

People who take proton pump inhibitor medicines at high doses for a long period of time (1 year or longer) may have an increased risk of fractures of the hip, wrist, or spine.

Proton pump inhibitors may reduce the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor or pharmacist about the possibility of vitamin B-12 deficiency if you have been taking a proton pump inhibitor for a long time (i.e. more than 3 years).

Other side effects not listed above may also occur in some people. Tell your doctor if you notice anything making you feel unwell when you are taking, or soon after you have finished taking PARIET.

Ask your doctor or pharmacist if you do not understand anything in this list.

After using PARIET

Storage

PARIET tablets are packaged in a double-sided aluminium blister strip.

Do not take PARIET tablets out of the blister pack until it is time to take them. If you take them out of the blister they may not keep well.

Keep PARIET tablets in a cool dry place where the temperature is below 25°C. Do not keep PARIET in the refrigerator or freezer.

Do not store PARIET, or any other medicine, in the bathroom or near a sink. Do not leave medicines in the car or on window sills. Heat and dampness can destroy some medicines.

Keep your medicines where children cannot reach them. A locked cupboard at least one-and-a-half metres (1.5 m) above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking PARIET tablets, or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets that are left over.

Product Description

What PARIET tablets look like:

PARIET 10 mg tablets are pink and have "E241" in black ink on one side.

PARIET 20 mg tablets are pale yellow, and have "E243" in red ink on one side.

PARIET 10 mg tablets are supplied in blister packs of 7 and 28 tablets.

PARIET 20 mg tablets are supplied in blister packs of 5 and 30 tablets

Ingredients

Each PARIET tablet contains 10 mg or 20 mg of rabeprazole sodium as the active ingredient.

Each tablet also contains the following other ingredients:

- mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax.
- the 20 mg tablets also contain yellow iron oxide (E172) and are printed with red ink (Edible Ink Red A1).
- the 10 mg tablets contain red iron oxide (E172) and are printed with gray ink (Edible Ink Gray F6).

The tablets do not contain lactose or gluten.

Sponsor

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Rd

Macquarie Park NSW 2113 Australia

Telephone: Toll Free 1800 226 334

Registration Numbers:

PARIET 10mg AUST R 76185

PARIET 20mg AUST R 76186

This leaflet was prepared in April 2016.

PARIET[®] is a trademark of Eisai Ltd.

PARIET[®] Tablets

PRODUCT INFORMATION

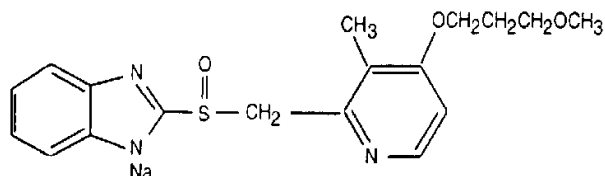
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red CI 77491 and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow CI 77492 and Edible Ink Red A1.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric PARIETal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ mL/min/1.73 m}^2$), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $\text{AUC}_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

CLINICAL TRIALS

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD

Percentage of Patients Healed		
Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD): The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD
Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers: In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p = 0.001$) after four weeks treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

**Table 3. Duodenal Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers: PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

**Table 4 Gastric Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

H. pylori eradication: In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxicillin 1g twice daily for a total of 7 days ($n = 83$), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxicillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ^{14}C -labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m^2) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Patients may need to be monitored when these drugs are taken together with PARIET.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema. Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including

thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **PRECAUTIONS**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal or hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET 10 mg are pink, biconvex tablets, marked with “ε 241” in black ink on one side. Supplied in blister packs of 28 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with “ε 243” in red ink on one side. Supplied in blisters pack of 5 and 30 tablets.

Storage Conditions

PARIET tablets should be stored below 25°C. Do not refrigerate or freeze.
Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG:

31 October 2000

DATE OF MOST RECENT AMENDMENT:

15 April 2016

® PARIET is a trademark of Eisai Ltd.

PARIET[®] Tablets

PRODUCT INFORMATION

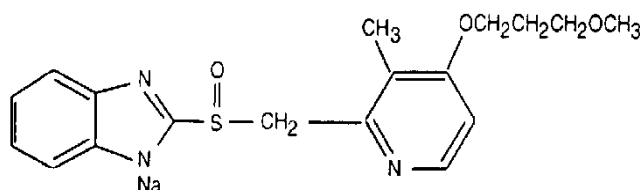
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red CI 77491 and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow CI 77492 and Edible Ink Red A1.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ mL/min/1.73 m}^2$), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $\text{AUC}_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

CLINICAL TRIALS

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD
Percentage of Patients Healed

Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD): The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD
Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers: In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p = 0.001$) after four weeks' treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days' treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

**Table 3. Duodenal Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers: PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

**Table 4 Gastric Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

***H. pylori* eradication:** In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxicillin 1g twice daily for a total of 7 days (n = 83), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxicillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET:

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clonidogrel: Clonidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clonidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clonidogrel should be discouraged.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema. Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.

Other: depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesaemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **PRECAUTIONS**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal or hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET 10 mg are pink, biconvex tablets, marked with “ε 241” in black ink on one side. Supplied in blister packs of 28 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with “ε 243” in red ink on one side. Supplied in blisters pack of 5 and 30 tablets.

Storage Conditions

PARIET tablets should be stored below 25°C. Do not refrigerate or freeze.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG:

31 October 2000

DATE OF MOST RECENT AMENDMENT:

18 May 2017

® PARIET is a trademark of Eisai Ltd.

PARIET[®] Tablets

PRODUCT INFORMATION

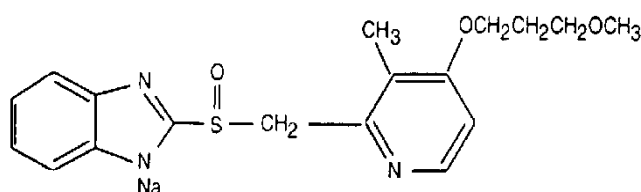
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow and Edible Ink Red A1.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ mL/min/1.73 m}^2$), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $\text{AUC}_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

CLINICAL TRIALS

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD
Percentage of Patients Healed

Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD): The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD
Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers: In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p = 0.001$) after four weeks' treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days' treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

**Table 3. Duodenal Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers: PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

**Table 4 Gastric Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

***H. pylori* eradication:** In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxicillin 1g twice daily for a total of 7 days (n = 83), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxicillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H. pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET:

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clonidogrel: Clonidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clonidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clonidogrel should be discouraged.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

Gastrointestinal: anorexia, gastritis, weight gain, stomatitis.

Skin: pruritis, sweating.

Special Senses: vision or taste disturbances.

Haematologic: leucocytosis.

Other: depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **PRECAUTIONS**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

Eradication of *H. pylori*: Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal or hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET 10 mg are pink, biconvex tablets, marked with “ε 241” in black ink on one side presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with “ε 243” in red ink on one side presented in blister packs of 7, 28 and 30 tablets.

Not all pack sizes may be supplied.

Storage Conditions

PARIET tablets should be stored below 25°C. Do not refrigerate.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG:

31 October 2000

DATE OF MOST RECENT AMENDMENT:

11 April 2018

® PARIET is a trademark of Eisai Ltd.

PARIET[®] Tablets

PRODUCT INFORMATION

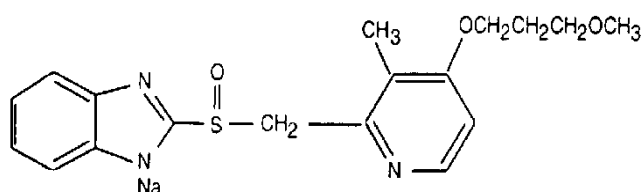
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow and Edible Ink Red A1.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ mL/min/1.73 m}^2$), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $\text{AUC}_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

CLINICAL TRIALS

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD
Percentage of Patients Healed

Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD): The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD
Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers: In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p = 0.001$) after four weeks' treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days' treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

**Table 3. Duodenal Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers: PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

**Table 4 Gastric Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

***H. pylori* eradication:** In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxicillin 1g twice daily for a total of 7 days (n = 83), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxicillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H. pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interference with Laboratory Tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. CgA increases due to decreased gastric acidity. To avoid this interference, proton pump inhibitors should be stopped 14 days before CgA measurements.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET:

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clonidogrel: Clonidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clonidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clonidogrel should be discouraged.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.

Other: depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesaemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **PRECAUTIONS**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxycillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal or hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET 10 mg are pink, biconvex tablets, marked with “ε 241” in black ink on one side presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with “ε 243” in red ink on one side presented in blister packs of 7, 28 and 30 tablets.

Not all pack sizes may be supplied.

Storage Conditions

PARIET tablets should be stored below 25°C. Do not refrigerate.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG:

31 October 2000

DATE OF MOST RECENT AMENDMENT:

27 July 2018

® PARIET is a trademark of Eisai Ltd.

PARIET[®] Tablets

PRODUCT INFORMATION

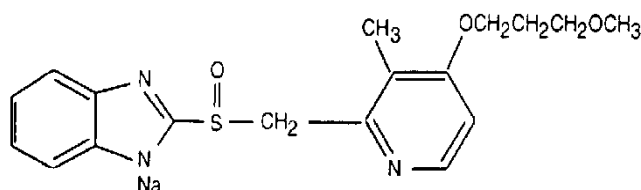
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow and Edible Ink Red A1.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Special populations

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ mL/min/1.73 m}^2$), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $\text{AUC}_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

CLINICAL TRIALS

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD
Percentage of Patients Healed

Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD): The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD
Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers: In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p = 0.001$) after four weeks' treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days' treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

**Table 3. Duodenal Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers: PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

**Table 4 Gastric Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

***H. pylori* eradication:** In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxicillin 1g twice daily for a total of 7 days (n = 83), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxicillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Fundic gland polyps

As with other PPIs, long-term use of rabeprazole is associated with an increased risk of fundic gland polyps (see **ADVERSE REACTIONS, Post-marketing data**). Patients with large or ulcerated polyps may be at risk of gastrointestinal bleeding or small intestinal blockage. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interference with Laboratory Tests

PPI-induced decreases in gastric acidity may lead to increases in serum chromogranin A (CgA) levels, which may lead to erroneous interpretations of laboratory results in investigations for neuroendocrine tumors. To avoid this interference, temporarily stop PARIET treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET:

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of rabeprazole based on the comprehensive assessment of the available adverse event information.

Clinical trials

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

Nervous System: headache, dizziness.

Gastrointestinal: diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.

Respiratory: rhinitis, pharyngitis, cough.

Musculoskeletal: non-specific pain, back pain, myalgia.

Skin: rash.

Other: asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience.

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **PRECAUTIONS**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

Eradication of *H. pylori*: Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal impairment.

Use in Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see PRECAUTIONS).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET 10 mg are pink, biconvex tablets, marked with “ε 241” in black ink on one side presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with “ε 243” in red ink on one side presented in blister packs of 7, 28 and 30 tablets.

Not all pack sizes may be supplied.

Storage Conditions

PARIET tablets should be stored below 25°C. Do not refrigerate.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG:

31 October 2000

DATE OF MOST RECENT AMENDMENT:

25 October 2018

® PARIET is a trademark of Eisai Ltd.

PARIET[®] Tablets

PRODUCT INFORMATION

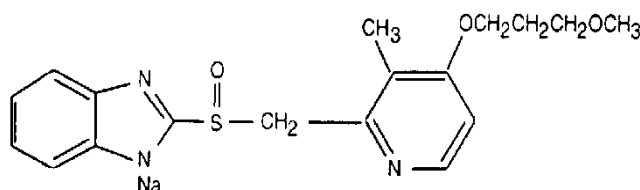
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow and Edible Ink Red A1.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Special populations

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ mL/min/1.73 m}^2$), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $\text{AUC}_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

CLINICAL TRIALS

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD
Percentage of Patients Healed

Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD): The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD
Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers: In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p = 0.001$) after four weeks' treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days' treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

**Table 3. Duodenal Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers: PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

**Table 4 Gastric Ulcers
Percentage of Patients Healed**

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

***H. pylori* eradication:** In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxicillin 1g twice daily for a total of 7 days (n = 83), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxicillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Fundic gland polyps

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

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H. pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interference with Laboratory Tests

PPI-induced decreases in gastric acidity may lead to increases in serum chromogranin A (CgA) levels, which may lead to erroneous interpretations of laboratory results in investigations for neuroendocrine tumors. To avoid this interference, temporarily stop PARIET treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET:

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of rabeprazole based on the comprehensive assessment of the available adverse event information.

Clinical trials

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

Nervous System: headache, dizziness.

Gastrointestinal: diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.

Respiratory: rhinitis, pharyngitis, cough.

Musculoskeletal: non-specific pain, back pain, myalgia.

Skin: rash.

Other: asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience.

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see **PRECAUTIONS**).

Gastrointestinal disorders

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

DOSAGE AND ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **PRECAUTIONS**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal impairment.

Use in Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

PARIET 10 mg are pink, biconvex tablets, marked with “ε 241” in black ink on one side presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with “ε 243” in red ink on one side presented in blister packs of 7, 28 and 30 tablets.

Not all pack sizes may be supplied.

Storage Conditions

PARIET tablets should be stored below 25°C. Do not refrigerate.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG:

31 October 2000

DATE OF MOST RECENT AMENDMENT:

17 June 2019

® PARIET is a trademark of Eisai Ltd.



PARIET[®]

RABEPRAZOLE SODIUM

AUSTRALIAN PRODUCT INFORMATION

1 NAME OF THE MEDICINE

Rabeprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

For the full list of excipients, see **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

PARIET 10 mg are pink, biconvex tablets, marked with "ε 241" in black ink on one side presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with "ε 243" in red ink on one side presented in blister packs of 7, 28 and 30 tablets.

Not all pack sizes may be supplied.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxycillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

4.2 DOSE AND METHOD OF ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal impairment.

Use in Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with hepatic impairment.

4.3 CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of

methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In such high-doses methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Fundic gland polyps

As with other PPIs, long-term use of rabeprazole is associated with an increased risk of fundic gland polyps (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Post-marketing data**). Most fundic gland polyps are asymptomatic. Patients with large or ulcerated polyps may be at risk of gastrointestinal bleeding or small intestinal blockage. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Use in hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Use in renal impairment

No data available

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

PPI-induced decreases in gastric acidity may lead to increases in serum chromogranin A (CgA) levels, which may lead to erroneous interpretations of laboratory results in investigations for neuroendocrine tumors. To avoid this interference, temporarily stop PARIET treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET:

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of rabeprazole based on the comprehensive assessment of the available adverse event information.

Clinical trials

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience.

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Gastrointestinal disorders

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors.

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H^+/K^+ -ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Mechanism of Action

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a

maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **5.3 PRECLINICAL SAFETY DATA**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Clinical trials

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD):

In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD

Percentage of Patients Healed

Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD):

The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD):

On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers:

In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers (p=0.001) after four weeks' treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency (p<0.001). After 7 days' treatment with PARIET 20 mg once daily, patients reported significantly less daytime (p=0.013) and night-time (p=0.003) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use (p<0.001).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks (p=0.002 and p=0.017 respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

Table 3. Duodenal Ulcers Percentage of Patients Healed

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly (p=0.038) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers:

PARIET was found to be significantly (p=0.002) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo (p<0.001).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily (n=184) and ranitidine 150 mg two times per day (n=180) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg (n=113) to omeprazole 20 mg (n=114), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

Table 4. Gastric Ulcers Percentage of Patients Healed

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

H. pylori eradication:

In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxicillin 1g twice daily for a total of 7 days ($n = 83$), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution

Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism

Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Excretion

Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary

excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Special populations

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC₀₋₂₄ was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, AUC_{0-∞} and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to **4.2 DOSE AND METHOD OF ADMINISTRATION** for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

5.3 PRECLINICAL SAFETY DATA

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

Genotoxicity

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Carcinogenicity

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow and Edible Ink Red A1.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

PARIET tablets should be stored below 25°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

PARIET 10 mg are presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are presented in blister packs of 7, 28 and 30 tablets.

Tablets are presented in an aluminium/aluminium blister.

Not all pack sizes may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

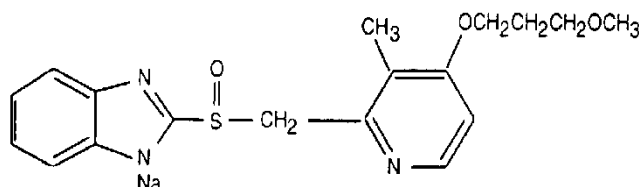
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers.

Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

Chemical structure



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS number

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8 SPONSOR

Janssen-Cilag Pty Ltd,

1-5 Khartoum Road,

Macquarie Park NSW 2113

Telephone: 1800 226 334

9 DATE OF FIRST APPROVAL

31 October 2000

10 DATE OF REVISION

22 June 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformat



PARIET®

RABEPRAZOLE SODIUM

AUSTRALIAN PRODUCT INFORMATION

1 NAME OF THE MEDICINE

Rabeprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

For the full list of excipients, see **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

PARIET 10 mg are pink, biconvex tablets, marked with "ε 241" in black ink on one side presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with "ε 243" in red ink on one side presented in blister packs of 7, 28 and 30 tablets.

Not all pack sizes may be supplied.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxycillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

4.2 DOSE AND METHOD OF ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal impairment.

Use in Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with hepatic impairment.

4.3 CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia 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 hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and then periodically while treatment continues (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as Clostridium difficile.

Subacute cutaneous lupus erythematosus

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

Fundic gland polyps

As with other PPIs, long-term use of rabeprazole is associated with an increased risk of fundic gland polyps (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Post-marketing data**). Most fundic gland polyps are asymptomatic. Patients with large or ulcerated polyps may be at risk of gastrointestinal bleeding or small intestinal blockage. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Use in hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Use in renal impairment

No data available

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

PPI-induced decreases in gastric acidity may lead to increases in serum chromogranin A (CgA) levels, which may lead to erroneous interpretations of laboratory results in investigations for neuroendocrine tumors. To avoid this interference, temporarily stop PARIET treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET:

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of rabeprazole based on the comprehensive assessment of the available adverse event information.

Clinical trials

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience.

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy. Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesaemia has also been reported rarely. Hypocalcaemia and/or hypokalaemia have been reported, which may be related to the occurrence of hypomagnesaemia (see **4.4 SPECIAL WARNINGS PRECAUTIONS FOR USE**)

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Gastrointestinal disorders

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors.

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H^+/K^+ -ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Mechanism of Action

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **5.3 PRECLINICAL SAFETY DATA**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Clinical trials

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD):

In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD

Percentage of Patients Healed

Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD):

The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD):

On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the

rabeprazole group ($p=0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers:

In a US study ($n=100$) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p=0.001$) after four weeks' treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days' treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

Table 3. Duodenal Ulcers Percentage of Patients Healed

Week	PARIET 20 mg od ($n=102$)	Omeprazole 20 mg od ($n=103$)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers:

PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg ($n=113$) to omeprazole 20 mg ($n=114$), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

Table 4. Gastric Ulcers Percentage of Patients Healed

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

H. pylori eradication:

In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxicillin 1g twice daily for a total of 7 days ($n = 83$), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

5.2 PHARMACOKINETIC PROPERTIES**Absorption**

PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution

Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism

Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Excretion

Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary

excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Special populations

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC₀₋₂₄ was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, AUC_{0-∞} and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to **4.2 DOSE AND METHOD OF ADMINISTRATION** for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

5.3 PRECLINICAL SAFETY DATA

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

Genotoxicity

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Carcinogenicity

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow and Edible Ink Red A1.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

PARIET tablets should be stored below 25°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

PARIET 10 mg are presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are presented in blister packs of 7, 28 and 30 tablets.

Tablets are presented in an aluminium/aluminium blister.

Not all pack sizes may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

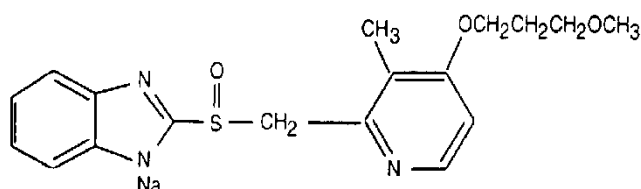
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name for rabeprazole sodium is ($\pm$) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers.

Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

Chemical structure



$C_{18}H_{20}N_3NaO_3S$

MW: 381.43

CAS number

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8 SPONSOR

Janssen-Cilag Pty Ltd,

1-5 Khartoum Road,

Macquarie Park NSW 2113

Telephone: 1800 226 334

9 DATE OF FIRST APPROVAL

31 October 2000

10 DATE OF REVISION

24 Nov 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of risk of hypocalcaemia and hypokalaemia related to hypomagnesaemia
4.8	Addition of risk of hypocalcaemia and hypokalaemia related to hypomagnesaemia



PARIET[®]

RABEPRAZOLE SODIUM

AUSTRALIAN PRODUCT INFORMATION

1 NAME OF THE MEDICINE

Rabeprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

For the full list of excipients, see **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

PARIET 10 mg are pink, biconvex tablets, marked with "ε 241" in black ink on one side presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with "ε 243" in red ink on one side presented in blister packs of 7, 28 and 30 tablets.

Not all pack sizes may be supplied.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxycillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

4.2 DOSE AND METHOD OF ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal impairment.

Use in Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with hepatic impairment.

4.3 CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia 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 hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and then periodically while treatment continues (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as Clostridium difficile.

Subacute cutaneous lupus erythematosus

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

Fundic gland polyps

As with other PPIs, long-term use of rabeprazole is associated with an increased risk of fundic gland polyps (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Post-marketing data**). Most fundic gland polyps are asymptomatic. Patients with large or ulcerated polyps may be at risk of gastrointestinal bleeding or small intestinal blockage. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Use in hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Use in renal impairment

No data available

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

PPI-induced decreases in gastric acidity may lead to increases in serum chromogranin A (CgA) levels, which may lead to erroneous interpretations of laboratory results in investigations for neuroendocrine tumors. To avoid this interference, temporarily stop PARIET treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET:

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of rabeprazole based on the comprehensive assessment of the available adverse event information.

Clinical trials

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience.

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy. Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesaemia has also been reported rarely. Hypocalcaemia and/or hypokalaemia have been reported, which may be related to the occurrence of hypomagnesaemia (see **4.4 SPECIAL WARNINGS PRECAUTIONS FOR USE**)

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Gastrointestinal disorders

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Metabolism and Nutrition disorders

Hyponatraemia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors.

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Mechanism of Action

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a

causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **5.3 PRECLINICAL SAFETY DATA**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Clinical trials

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD):

In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole

in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD

Percentage of Patients Healed

Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD):

The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD):

On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control.

Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p<0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p=0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers:

In a US study ($n=100$) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers ($p=0.001$) after four weeks' treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency ($p<0.001$). After 7 days' treatment with PARIET 20 mg once daily, patients reported significantly less daytime ($p=0.013$) and night-time ($p=0.003$) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use ($p<0.001$).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks ($p=0.002$ and $p=0.017$ respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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 ($p=0.037$).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

Table 3. Duodenal Ulcers Percentage of Patients Healed

Week	PARIET 20 mg od ($n=102$)	Omeprazole 20 mg od ($n=103$)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly ($p=0.038$) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers:

PARIET was found to be significantly ($p=0.002$) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo ($p<0.001$).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily ($n=184$) and ranitidine 150 mg two times per day ($n=180$) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg (n=113) to omeprazole 20 mg (n=114), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

Table 4. Gastric Ulcers Percentage of Patients Healed

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

H. pylori eradication:

In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxicillin 1g twice daily for a total of 7 days (n = 83), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution

Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism

Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Excretion

Following a single 20 mg ¹⁴C-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 the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Special populations

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC₀₋₂₄ was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, AUC_{0-∞} and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to **4.2 DOSE AND METHOD OF ADMINISTRATION** for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

5.3 PRECLINICAL SAFETY DATA

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

Genotoxicity

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Carcinogenicity

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow and Edible Ink Red A1.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

PARIET tablets should be stored below 25°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

PARIET 10 mg are presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are presented in blister packs of 7, 28 and 30 tablets.

Tablets are presented in an aluminium/aluminium blister.

Not all pack sizes may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

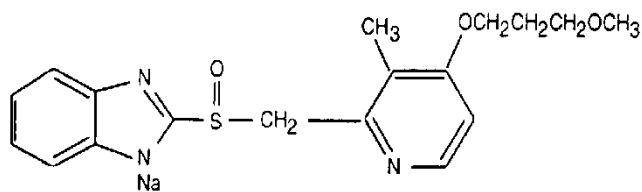
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers.

Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

Chemical structure



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS number

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8 SPONSOR

Janssen-Cilag Pty Ltd,
1-5 Khartoum Road,
Macquarie Park NSW 2113
Telephone: 1800 226 334

9 DATE OF FIRST APPROVAL

31 October 2000

10 DATE OF REVISION

12 August 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Addition of risk of hyponatraemia



PARIET[®]

RABEPRAZOLE SODIUM

AUSTRALIAN PRODUCT INFORMATION

1 NAME OF THE MEDICINE

Rabeprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PARIET is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole) or 20 mg rabeprazole sodium (equivalent to 18.85 mg rabeprazole).

For the full list of excipients, see **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

PARIET 10 mg are pink, biconvex tablets, marked with "ε 241" in black ink on one side presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are light yellow, biconvex tablets, marked with "ε 243" in red ink on one side presented in blister packs of 7, 28 and 30 tablets.

Not all pack sizes may be supplied.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PARIET is indicated for:

- Treatment and prevention of relapse of gastro-oesophageal reflux disease
- Symptomatic treatment of gastro-oesophageal reflux disease
- Treatment of duodenal ulcers
- Treatment of gastric ulcers.

Patients whose gastric and duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) usually require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

PARIET is also indicated, in combination with clarithromycin and amoxycillin, for:

- Eradication of *Helicobacter pylori* in patients with peptic ulcer disease or chronic gastritis
- Healing of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

4.2 DOSE AND METHOD OF ADMINISTRATION

PARIET tablets should not be chewed or crushed, but should be swallowed whole. PARIET tablets should be taken at the same time each day to facilitate treatment compliance. PARIET was taken with or without food in the pivotal clinical trials.

Adults

Treatment of active Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is one 20 mg tablet to be taken once daily for four to eight weeks.

Prevention of Relapse of Gastro-oesophageal Reflux Disease (GORD): The recommended oral dose for preventing relapse of GORD, once healing is achieved, is one 10 mg tablet to be taken once daily.

If needed this dose should be increased to one 20 mg tablet to be taken once daily.

Symptomatic Treatment of Gastro-Oesophageal Reflux Disease (GORD): Treatment should commence at 10 mg once daily in patients without oesophagitis. If no response, the dose should be increased to 20 mg once daily for four weeks. If symptom control has not been achieved within four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen of one 10 mg tablet to be taken once daily, when needed. (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Treatment of active Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is one 20 mg tablet to be taken once daily.

Some patients with duodenal ulcer may respond to one 10 mg tablet taken once daily.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Most patients with gastric ulcer heal within six weeks. However, again a few patients may require an additional six weeks of therapy to achieve healing.

*Eradication of *H. pylori*:* Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with: PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days.

Eradication of *H. pylori* with this regimen has been shown to result in the healing of duodenal or gastric ulcers without the need for continued ulcer therapy.

Use in Children

PARIET is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal impairment.

Use in Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with hepatic impairment.

4.3 CONTRAINDICATIONS

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic response to therapy with PARIET does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET.

Patients using an on-demand regimen for symptomatic GORD should be further reviewed and/or investigated if symptoms persist beyond 6 months.

Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue rabeprazole sodium if acute tubulointerstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia 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 hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and then periodically while treatment continues (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as Clostridium difficile.

Subacute cutaneous lupus erythematosus

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

Fundic gland polyps

As with other PPIs, long-term use of rabeprazole is associated with an increased risk of fundic gland polyps (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Post-marketing data**). Most fundic gland polyps are asymptomatic. Patients with large or ulcerated polyps may be at risk of gastrointestinal bleeding or small intestinal blockage. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Use in hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Use in renal impairment

No data available

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

PPI-induced decreases in gastric acidity may lead to increases in serum chromogranin A (CgA) levels, which may lead to erroneous interpretations of laboratory results in investigations for neuroendocrine tumors. To avoid this interference, temporarily stop PARIET treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of rabeprazole sodium on other drugs – demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET:

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir: co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Effect of rabeprazole sodium on other drugs – theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs – potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxycillin (as single and multiple oral doses).

Taking PARIET with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of rabeprazole based on the comprehensive assessment of the available adverse event information.

Clinical trials

PARIET was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the PARIET treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of PARIET.

The adverse events, which may or may not be causally related to PARIET, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

Nervous System: headache, dizziness.
Gastrointestinal: diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
Respiratory: rhinitis, pharyngitis, cough.
Musculoskeletal: non-specific pain, back pain, myalgia.
Skin: rash.
Other: asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

Gastrointestinal: dyspepsia, eructation, dry mouth.
Respiratory: sinusitis, bronchitis.
Musculoskeletal: arthralgia, leg cramps.
Urinary: urinary tract infection.
Other: fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

Gastrointestinal: anorexia, gastritis, weight gain, stomatitis.
Skin: pruritis, sweating.
Special Senses: vision or taste disturbances.
Haematologic: leucocytosis.
Other: depression.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience.

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy.

Erythema multiforme, tubulointerstitial nephritis (with possible progression to renal failure), gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesaemia has also been reported rarely. Hypocalcaemia and/or hypokalaemia have been reported, which may be related to the occurrence of hypomagnesaemia (see **4.4 SPECIAL WARNINGS PRECAUTIONS FOR USE**)

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Gastrointestinal disorders

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Metabolism and Nutrition disorders

Hyponatraemia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors.

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Mechanism of Action

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Helicobacter pylori is associated with duodenal and gastric ulcer disease in approximately 95% and 70% of patients respectively. *H. pylori* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. *H. pylori* eradication therapy is

appropriate in most patients with duodenal and gastric ulcer where the latter is not caused by nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **5.3 PRECLINICAL SAFETY DATA**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Clinical trials

At the time of registration, more than 3000 patients in the US, Europe and Japan had received rabeprazole sodium in both controlled and uncontrolled clinical studies.

The efficacy of PARIET was assessed in nine double-blind, controlled, randomised, parallel group primary efficacy trials in patients with duodenal ulcer, gastric ulcer and gastro-oesophageal reflux disease. Three trials were conducted in each indication, a placebo controlled study and comparative studies with either ranitidine or omeprazole. In all these studies the primary efficacy variable used was ulcer or ulcerative GORD healing rates as determined by endoscopic examination.

A further three clinical trials were conducted to establish efficacy of rabeprazole in the long-term prevention of relapse of gastro-oesophageal reflux disease. Two studies were placebo controlled, whilst the other was actively controlled with omeprazole. In all three studies the primary efficacy variable used was the continued absence of oesophageal erosions or ulcerations as determined by endoscopic examination.

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD):

In the placebo-controlled study, 103 patients were treated for up to eight weeks either with placebo or PARIET 10, 20 or 40 mg once daily (od). PARIET was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment ($p < 0.001$).

PARIET 20 mg once daily was also significantly more effective than placebo in terms of symptom relief, providing complete resolution of heartburn frequency, daytime heartburn severity, and decreasing the amount of antacid taken per day after four and eight weeks of treatment.

PARIET 20 mg once daily was statistically superior to ranitidine 150 mg four times per day with respect to the percentage of patients healed at endoscopy and in symptom relief. PARIET was also significantly more effective than ranitidine in terms of providing complete resolution of heartburn frequency, and daytime and night-time heartburn severity; after four and eight weeks of treatment.

In an active-controlled study of 202 patients treated with PARIET 20 mg once daily or omeprazole 20 mg once daily for up to eight weeks, PARIET was as effective as omeprazole in producing endoscopic healing. The percentages of patients healed at endoscopy at four and eight weeks are given in Table 1.

Table 1. Erosive or Ulcerative GORD

Percentage of Patients Healed

Week	PARIET 20 mg od (n=100)	Omeprazole 20 mg od (n=102)
4	81%	81%
8	92%	94%

PARIET 20 mg once daily was also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, in improving daytime and night-time heartburn severity, and in reducing the amount of antacid taken per day.

Prevention of Relapse of Gastro-Oesophageal Reflux Disease (GORD):

The prevention of relapse in patients with erosive or ulcerative GORD previously healed with gastric anti-secretory therapy was assessed in two U.S. multi-centre, double-blind, placebo-controlled studies of 52 weeks duration. The two studies of identical design randomised 209 and 285 patients respectively, to receive either 10 mg or 20 mg of PARIET, or placebo once daily. In both studies PARIET was significantly superior to placebo in prevention of relapse of GORD.

In both multicentre trials, PARIET 10 mg once daily and 20 mg once daily were significantly more effective than placebo in preventing the recurrence of heartburn frequency ($p < 0.001$) as well as improving day-time ($p < 0.001$) and night-time ($p \leq 0.003$) heartburn severity.

In the actively controlled European study, 243 patients were treated with a fixed dose of either omeprazole 20 mg once daily, or PARIET 10 mg or 20 mg once daily. Treatment with both 10 mg and 20 mg PARIET were as effective as omeprazole 20 mg in preventing GORD relapse ($p = 0.5216$ and $p = 0.8004$ respectively). See Table 2.

Table 2. Erosive or Ulcerative GORD Percentage of Patients Relapse Free

Week	PARIET 10 mg od (n=82)	PARIET 20 mg od (n=78)	Omeprazole 20 mg od (n=83)
52	95%	96%	95%

PARIET 10 mg and 20 mg once daily were also as effective as omeprazole 20 mg once daily in reducing heartburn frequency, and improving daytime and night-time heartburn severity.

Symptomatic Gastro-Oesophageal Reflux Disease (GORD):

On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

Treatment of Duodenal Ulcers:

In a US study (n=100) PARIET 20 mg once daily was significantly superior to placebo in producing healing of endoscopically defined duodenal ulcers (p=0.001) after four weeks' treatment

Patients treated for four weeks with PARIET 20 mg once daily reported significantly less ulcer pain frequency (p<0.001). After 7 days' treatment with PARIET 20 mg once daily, patients reported significantly less daytime (p=0.013) and night-time (p=0.003) ulcer pain severity than patients treated with placebo. This difference continued for the whole study period. Additionally, PARIET 20 mg once daily was significantly more effective than placebo in reducing daily antacid use (p<0.001).

In the ranitidine-controlled trial, 375 patients with endoscopically defined duodenal ulcers were treated with PARIET 20 mg once daily or ranitidine 150 mg twice daily for up to four weeks. PARIET 20 mg once daily was significantly more effective than ranitidine 150 mg twice daily at producing complete healing of duodenal ulcers after 2 and 4 weeks (p=0.002 and p=0.017 respectively).

PARIET 20 mg once daily was also significantly more effective than ranitidine 150 mg twice daily 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).

In patients with endoscopically defined duodenal ulcers treated for up to four weeks, PARIET 20 mg once daily was as effective as omeprazole 20 mg once daily in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are shown in Table 3.

Table 3. Duodenal Ulcers Percentage of Patients Healed

Week	PARIET 20 mg od (n=102)	Omeprazole 20 mg od (n=103)
2	69%	61%
4	98%	93%

PARIET 20 mg once daily was significantly (p=0.038) more effective than omeprazole 20 mg once daily in reducing daytime ulcer pain severity at week 4. In this trial PARIET 20 mg once daily also proved to be as effective as omeprazole 20 mg once daily at reducing ulcer pain frequency and night-time ulcer pain.

Treatment of Gastric Ulcers:

PARIET was found to be significantly (p=0.002) superior to placebo in producing endoscopically defined healing of gastric ulcers after 6 weeks in a placebo-controlled study assessing the effectiveness of PARIET 20 mg once daily versus placebo (p<0.001).

The rates of endoscopic healing of gastric ulcers in patients treated with PARIET 20 mg once daily (n=184) and ranitidine 150 mg two times per day (n=180) were found to be equivalent after three and six weeks of treatment.

In a European multicentre study comparing PARIET 20 mg (n=113) to omeprazole 20 mg (n=114), the rates of endoscopic healing of gastric ulcers were found to be equivalent with the two treatments at three and six weeks. See Table 4.

Table 4. Gastric Ulcers Percentage of Patients Healed

Week	PARIET 20 mg od (n=143)	Omeprazole 20 mg od (n=114)
3	58%	61%
6	91%	91%

PARIET was significantly superior to omeprazole 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 night-time ulcer pain severity (week 6, $p=0.022$).

H. pylori eradication:

In a multicentre, randomised, controlled European study conducted to establish the efficacy of PARIET based triple therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination: PARIET 20mg twice daily with clarithromycin 500mg twice daily and amoxycillin 1g twice daily for a total of 7 days ($n = 83$), achieved an eradication rate of 94% and a healing rate for duodenal ulcers of 91%.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

PARIET tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution

Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism

Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Excretion

Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Special populations

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC₀₋₂₄ was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, AUC_{0-∞} and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to **4.2 DOSE AND METHOD OF ADMINISTRATION** for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

5.3 PRECLINICAL SAFETY DATA

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day, the maximum recommended PARIET dose for the treatment of GORD and active gastro-duodenal ulcers. For *H pylori* eradication, the recommended dose of PARIET is 40 mg/day (20mg b.i.d.) for one week; this should be taken into account when reviewing exposure figures.

Genotoxicity

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Carcinogenicity

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at the recommended dose for GORD (20 mg/day).

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

PARIET tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red and Edible Ink Gray F6 and the 20 mg tablet contains iron oxide yellow and Edible Ink Red A1.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

PARIET tablets should be stored below 25°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

PARIET 10 mg are presented in blister packs of 7 (starter pack only), 28 and 30 tablets.

PARIET 20 mg are presented in blister packs of 7, 28 and 30 tablets.

Tablets are presented in an aluminium/aluminium blister.

Not all pack sizes may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

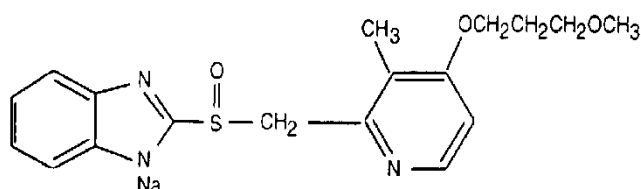
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name for rabeprazole sodium is ($\pm$) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers.

Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

Chemical structure



$C_{18}H_{20}N_3NaO_3S$

MW: 381.43

CAS number

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8 SPONSOR

Janssen-Cilag Pty Ltd,

1-5 Khartoum Road,

Macquarie Park NSW 2113

Telephone: 1800 226 334

9 DATE OF FIRST APPROVAL

31 October 2000

10 DATE OF REVISION

08 November 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Updates to risk of acute tubulointerstitial nephritis and possible progression to renal failure
4.8	Addition of risk of tubulointerstitial nephritis

PARIET 10[®] Tablets

PRODUCT INFORMATION

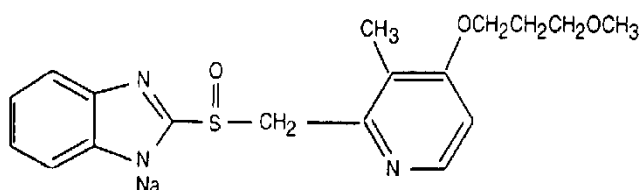
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



$C_{18}H_{20}N_3NaO_3S$

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET 10 is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole).

PARIET 10 tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax, iron oxide red CI 77491 and Edible Ink Gray F6.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H^+/K^+ -ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET 10 tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC₀₋₂₄ was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, AUC_{0-∞} and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

Clinical trials

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) (p<0.00001).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group (p=0.0011). Treatment failure was associated with an increased antacid consumption.

The efficacy of rabeprazole 10 mg or 20 mg daily versus placebo was assessed in a randomised, double blind, parallel group study (n=199) over a four week interval in subjects with moderately severe gastro-oesophageal reflux disease and grade 0 or 1 oesophagitis at endoscopy. The primary efficacy variable was defined as the time in days for subjects to achieve their first 24 hour interval without heartburn. Results showed that the average times were 6.541 +/- 0.923 days for rabeprazole 10 mg, 10 +/- 1.258 days for rabeprazole 20 mg and 16.347 +/- 1.105 days placebo. There was no significant difference between the rabeprazole groups.

INDICATIONS

PARIET 10 is indicated for:

- Symptomatic relief of heartburn and other symptoms of gastro-oesophageal reflux disease

CONTRAINDICATIONS

PARIET 10 is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET 10 does not preclude the presence of gastric malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET 10.

Patients on PARIET 10 should be further reviewed and/or investigated if symptoms persist or recur within 2 weeks of completing the course.

Patients should be referred to their doctor for review if:

- they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- they have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- they are being treated for symptomatic GORD and require PARIET 10 for more than 14 days.
- they have any other significant medical condition.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET 10 is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Patients should be referred to their doctor for review if they have severe hepatic impairment (eg. cirrhosis)

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day.,

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at 20 mg/day.

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively, and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195-or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interactions with Other Drugs

Effect of rabeprazole sodium on other drugs - demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir. Co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET 10 should not be co-administered with atazanavir.

Patients may need to be monitored when these drugs are taken together with PARIET 10.

Effect of rabeprazole sodium on other drugs - theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs - potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET 10 with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Rabeprazole was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the rabeprazole treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of rabeprazole.

The adverse events, which may or may not be causally related to rabeprazole, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with rabeprazole. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome.

DOSAGE AND ADMINISTRATION

Adults 18 years of age and over:

The recommended dose is one tablet per day to be taken at the same time each day (to facilitate treatment compliance) for at least 7 days and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with PARIET 10, patients should be referred to their doctor. PARIET 10 tablets should not be chewed or crushed, but should be swallowed whole.

Use in Children under 18 years of age

PARIET 10 is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION

PARIET 10 tablets are pink, biconvex tablets, marked with "ε 241" in black ink on one side. Supplied in blister packs of 7 and 14 tablets.

Storage

PARIET 10 tablets should be stored below 25°C. Do not refrigerate or freeze.

Tablets are presented in an aluminium/aluminium blister.

Schedule

PARIET 10 in packs of 7 and 14 tablets are Schedule 3 – Pharmacist Only Medicine.

SPONSOR

Johnson & Johnson Pacific Pty Ltd.
45 Jones Street
Ultimo NSW 2007
Australia

Date of TGA approval: XXXX

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PARIET[®] 10 Tablets

Rabeprazole sodium

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about PARIET 10 tablets. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor or pharmacist has weighed the risks of you taking PARIET 10 against the benefits this medicine is expected to have for you. **If you have any concerns about using PARIET 10 ask your doctor or pharmacist.**

Keep this leaflet with your medicine. You may need to read it again.

What PARIET 10 is used for

The name of your medicine is PARIET 10. It contains the active ingredient rabeprazole sodium.

PARIET 10 is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastroesophageal reflux.

This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn. Frequent heartburn is when you have heartburn for two or more days a week. Heartburn that occurs frequently is a typical symptom of gastroesophageal reflux disease (GORD).

Who should use PARIET 10

PARIET 10 is recommended for adults 18 years or over suffering from heartburn or acid reflux at least 2 times a week. PARIET 10 is not the right medicine for you if you suffer heartburn or acid reflux only occasionally (one episode of heartburn or acid reflux a week or less), or if you want immediate relief of heartburn.

How PARIET 10 works

PARIET 10 belongs to a group of medicines called proton pump inhibitors (PPIs). PARIET 10 works by decreasing the amount of acid the stomach makes, to give relief from the symptoms. Your food will still be digested in the normal way.

PARIET 10 will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take PARIET 10 for a few days before experiencing the full effect.

There is no evidence that PARIET 10 is addictive.

PARIET 10 is only available from your pharmacist or doctor.

Before you take PARIET 10

When you must not take it:

Do not take PARIET 10 if you have an allergy to:

- rabeprazole sodium
- any of the ingredients listed at the end of this leaflet.
- other proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole).

Symptoms of an allergic reaction may include:

- rash, itching or hives on the skin
- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body

- **Do not take PARIET 10 if you have severe liver disease or cirrhosis.**

- **Do not take PARIET 10 if the packaging is torn or shows signs of tampering.**

- **Do not take PARIET 10 after the expiry date (EXP) printed on the pack has passed.**

PARIET 10 should not be given to children and adolescents under 18 years of age.

Safety and effectiveness of PARIET 10 in children has not been established.

If you are not sure whether you should start taking PARIET 10 alone or in combination with any other medications talk to your doctor or pharmacist.

Before you start to take it:

You must tell your pharmacist or doctor if:

- you are pregnant or intend to become pregnant.
- you are breast-feeding or intend to breast-feed. It is not known if PARIET 10 passes into breast milk.
- you have or have ever had liver disease.
- you have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you have jaundice, liver problems, anaemia, previous gastric ulcer or gastrointestinal surgery.
- you have new or recently changed symptoms including persistent vomiting or vomiting of blood, blood in the stools or unexplained weight loss.

If you have suffered from frequent heartburn / indigestion symptoms for some time you should see your doctor.

You should also speak to your doctor before taking PARIET 10 if you are due to have an endoscopy (a special test ordered by your doctor).

Taking other medicines:

Tell your doctor or pharmacist if you are taking any other medicines, including medicines you can buy without a prescription from a pharmacy, supermarket or health food shop.

In particular, tell your doctor or pharmacist if you are taking any of the following:

- digoxin, a medicine used to treat heart problems.
- ketoconazole, a medicine used to treat fungal infections.
- Clarithromycin, a medicine used to treat infection.
- Atazanavir, a medicine used to treat viral infections.
- Clopidogrel, an antiplatelet medicine.

These medicines may be affected by PARIET 10 or may affect how well PARIET 10 works. Your doctor or pharmacist can tell you what to do if you are taking any other medicines.

If you have not told your doctor or pharmacist about any of the above, tell them before you start taking PARIET 10 ADVANCE.

Taking PARIET 10

How much to take:

Adults

The usual dose is one tablet at the same time each day.

Children

PARIET 10 should not be given to children or adolescents under 18 years of age.

How to take it:

- PARIET 10 should be swallowed whole, with a glass of water or other liquid.
- Do NOT crush or chew the tablets. They have a special coating, which protects them from the acid in your stomach. If the coating is broken by chewing, the tablets may not work.
- It does not matter if you take PARIET 10 with food or on an empty stomach.

Ask your doctor or pharmacist for help if you do not understand the instructions provided with this medicine.

How long to take it

Take one tablet daily for at least 7 days and up to 14 days. You should not take it for more than 14 days unless directed by a doctor.

If you forget to take it:

If you forget to take your tablet take it as soon as you remember, and then continue to take it as you would normally.

However, if it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you are not sure what to do, check with your doctor or pharmacist.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you have taken too much (overdose):

Immediately telephone your doctor or the Poisons Information Centre for advice, or go to Accident and Emergency at your nearest hospital.

Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

Poisons Information Centre telephone numbers:

- Australia: 13 11 26
- New Zealand: 0800 POISON or 0800 764 766

Keep these telephone numbers handy.

While you are using PARIET 10

Things you must do:

- Use PARIET 10 exactly as your doctor or pharmacist has advised.
- Always swallow PARIET 10 tablets whole.
- Tell your doctor if you become pregnant while you are taking PARIET 10.
- Tell your doctor or pharmacist if you do not feel better while taking PARIET 10. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

Tell your doctor or pharmacist that you are taking PARIET 10 if you are about to start taking a new medicine.

Things you must not do:

- Do not use PARIET 10 to treat any other complaint unless your doctor says to.
- Do not give this medicine to anyone else, even if they have the same symptoms as you.
- Do not crush or chew the tablets.
- Do not give PARIET 10 to children under 18 years of age.

Things that may help your condition

Some self help measures suggested below may help your condition. Talk to your doctor or pharmacist for more information about these measures.

- **Alcohol** - your doctor may advise you to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis/period pain/headaches** - these medicines may irritate the stomach and may make your condition worse. Your doctor or pharmacist may suggest other medicines you can take.

- **Caffeine** - your doctor may advise you to limit the number of drinks which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits** - eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **Smoking** - your doctor may advise you to stop smoking or at least cut down.
- **Weight** - your doctor may suggest losing some weight to help your condition.

Side Effects

PARIET 10 is usually well tolerated but tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking PARIET 10.

PARIET 10 helps most people with frequent heartburn, but it may have unwanted side effects in a few people.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some side effects.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor if you experience any of the following and they worry you:

- headache
- dizziness
- diarrhoea
- constipation
- stomach pain
- muscle weakness
- flatulence
- dry mouth
- breast enlargement in men
- itchy rash accompanied by skin eruption

These side effects are usually mild.

Tell your doctor immediately if you notice any of the following:

- bleeding or bruising more easily than normal
- signs of frequent infections such as fever, severe chills, sore throat or mouth ulcers.

These are serious side effects. You may need urgent medical attention. Serious side effects are rare.

Tell your doctor immediately and do not take your next dose of PARIET 10 if you experience:

- signs of allergy such as skin rash, reddening, blisters or itching, swelling of the face, lips or other parts of the body, shortness of breath or wheezing.

Other side effects not listed above may also occur in some people. Tell your doctor if you notice anything making you feel unwell when you are taking, or soon after you have finished taking PARIET 10.

For this reason contact your doctor or pharmacist immediately if you notice any of the following:

- pain or indigestion
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

Ask your doctor or pharmacist if you do not understand anything in this list.

After using PARIET 10

Storage

PARIET 10 tablets are packaged in a double-sided aluminium blister strip.

Do not take PARIET 10 tablets out of the blister pack until it is time to take them. If you take them out of the blister they may not keep well.

Keep PARIET 10 tablets in a cool dry place where the temperature is below 25°C. Do not keep PARIET 10 in the refrigerator.

Do not store PARIET 10, or any other medicine, in the bathroom or near a sink. Do not leave medicines in the car or on window sills. Heat and dampness can destroy some medicines.

Keep your medicines where children cannot reach them. A locked cupboard at least one-and-a-half metres (1.5 m) above the ground is a good place to store medicines.

Disposal

If your doctor or pharmacist tells you to stop taking PARIET 10 tablets, or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets that are left over.

Product Description

What PARIET 10 tablets look like:

The tablets are pink and have “E241” in black ink marked on one side.

The tablets are supplied in blister packs of 7 and 14 tablets.

Ingredients

Each PARIET 10 tablet contains 10 mg of rabeprazole sodium as the active ingredient.

Each tablet also contains the following other ingredients:

- mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax.
- red iron oxide (E172) and are printed with gray ink (Edible Ink Gray F6).
- the tablets do not contain lactose or gluten.

Sponsor

Johnson and Johnson Pacific
45 Jones Street
Ultimo NSW 2007
ARTG Number: Aust R XXXX

For further information call our toll free numbers
AUS: 1800 029 979
NZ: 0800446 147

This leaflet was prepared in September 2009

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PARIET 10[®] Tablets

PRODUCT INFORMATION

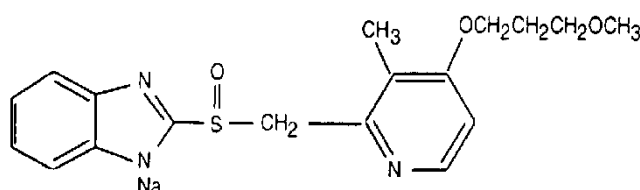
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



$C_{18}H_{20}N_3NaO_3S$

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET 10 is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole).

PARIET 10 tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax, iron oxide red CI 77491 and Edible Ink Gray F6.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H^+/K^+ -ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

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Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

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In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, AUC_{0-∞} and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

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Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group (p=0.0011). Treatment failure was associated with an increased antacid consumption.

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Patients on PARIET 10 should be further reviewed and/or investigated if symptoms persist or recur within 2 weeks of completing the course.

Patients should be referred to their doctor for review if:

- they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- they have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- they are being treated for symptomatic GORD and require PARIET 10 for more than 14 days.
- they have any other significant medical condition.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET 10 is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Patients should be referred to their doctor for review if they have severe hepatic impairment (eg. cirrhosis).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at 20 mg/day.

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively), and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interactions with Other Drugs

Effect of rabeprazole sodium on other drugs - demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Clonidogrel: Clonidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clonidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clonidogrel should be discouraged.

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir. Co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET 10 should not be co-administered with atazanavir.

Patients may need to be monitored when these drugs are taken together with PARIET 10.

Effect of rabeprazole sodium on other drugs - theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs - potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET 10 with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Rabeprazole was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the rabeprazole treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of rabeprazole.

The adverse events, which may or may not be causally related to rabeprazole, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

Nervous System: headache, dizziness.

Gastrointestinal: diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.

Respiratory: rhinitis, pharyngitis, cough.
Musculoskeletal: non-specific pain, back pain, myalgia.
Skin: rash.
Other: asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

Gastrointestinal: dyspepsia, eructation, dry mouth.
Respiratory: sinusitis, bronchitis.
Musculoskeletal: arthralgia, leg cramps.
Urinary: urinary tract infection.

***Other:* fever, nervousness, somnolence, chills, peripheral oedema.**

Rare ($\geq 0.01\%$ and $< 0.1\%$)

Gastrointestinal: anorexia, gastritis, weight gain, stomatitis.
Skin: pruritis, sweating.
Special Senses: vision or taste disturbances.
Haematologic: leucocytosis.
Other: depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with rabeprazole. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome.

There have been post-marketing reports of bone fractures (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Adults 18 years of age and over:

The recommended dose is one tablet per day to be taken at the same time each day (to facilitate treatment compliance) for at least 7 days and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with PARIET 10, patients should be referred to their doctor. PARIET 10 tablets should not be chewed or crushed, but should be swallowed whole. PARIET 10 tablets were taken with or without food in the pivotal clinical trials.

Use in Children under 18 years of age

PARIET 10 is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION

PARIET 10 tablets are pink, biconvex tablets, marked with “E 241” in black ink on one side. Supplied in blister packs of 7 and 14 tablets.

Storage

PARIET 10 tablets should be stored below 25°C. Do not refrigerate or freeze.

Tablets are presented in an aluminium/aluminium blister.

Schedule

PARIET 10 in packs of 7 and 14 tablets are Schedule 3 – Pharmacist Only Medicine.

SPONSOR

Janssen-Cilag Pty Ltd.
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

Date of TGA approval: 01 April 2010

Date of most recent amendment:

® PARIET is a trademark of Eisai Ltd.

PARIET 10[®] Tablets

PRODUCT INFORMATION

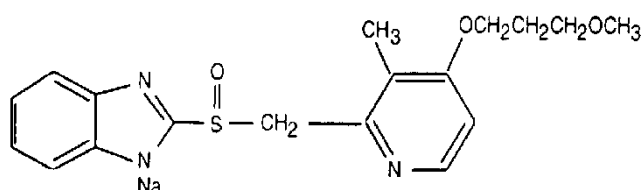
NAME OF THE DRUG

Rabeprazole sodium

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- they are being treated for symptomatic GORD and require PARIET 10 for more than 14 days.
- they have any other significant medical condition.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET 10 is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Patients should be referred to their doctor for review if they have severe hepatic impairment (eg. cirrhosis).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at 20 mg/day.

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively, and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs - demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Clonidogrel: Clonidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clonidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clonidogrel should be discouraged.

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir. Co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET 10 should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Patients may need to be monitored when these drugs are taken together with PARIET 10.

Effect of rabeprazole sodium on other drugs - theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs - potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET 10 with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Rabeprazole was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the rabeprazole treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of rabeprazole.

The adverse events, which may or may not be causally related to rabeprazole, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with rabeprazole. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome.

There have been post-marketing reports of bone fractures (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Adults 18 years of age and over:

The recommended dose is one tablet per day to be taken at the same time each day (to facilitate treatment compliance) for at least 7 days and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with PARIET 10, patients should be referred to their doctor. PARIET 10 tablets should not be chewed or crushed, but should be swallowed whole. PARIET 10 tablets were taken with or without food in the pivotal clinical trials.

Use in Children under 18 years of age

PARIET 10 is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET 10 tablets are pink, biconvex tablets, marked with “ε 241” in black ink on one side. Supplied in blister packs of 7 and 14 tablets.

Storage Conditions

PARIET 10 tablets should be stored below 25°C. Do not refrigerate or freeze.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

Janssen-Cilag Pty Ltd.
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 3 – Pharmacist Only Medicine.

DATE OF FIRST INCLUSION IN THE ARTG

01 April 2010

DATE OF MOST RECENT AMENDMENT

TBA

® PARIET is a trademark of Eisai Ltd.

PARIET 10[®] Tablets

PRODUCT INFORMATION

FOI 26-2974 - Document 19

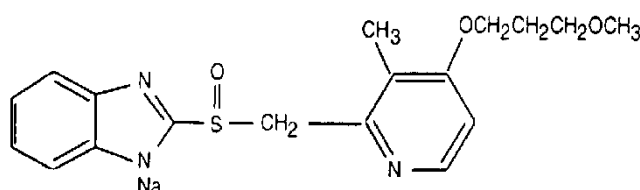
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET 10 is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole).

PARIET 10 tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax, iron oxide red CI 77491 and Edible Ink Gray F6.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET 10 tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC₀₋₂₄ was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, AUC_{0-∞} and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

Clinical trials

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) (p<0.00001).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group (p=0.0011). Treatment failure was associated with an increased antacid consumption.

The efficacy of rabeprazole 10 mg or 20 mg daily versus placebo was assessed in a randomised, double blind, parallel group study (n=199) over a four week interval in subjects with moderately severe gastro-oesophageal reflux disease and grade 0 or 1 oesophagitis at endoscopy. The primary efficacy variable was defined as the time in days for subjects to achieve their first 24 hour interval without heartburn. Results showed that the average times were 6.541 +/- 0.923 days for rabeprazole 10 mg, 10 +/- 1.258 days for rabeprazole 20 mg and 16.347 +/- 1.105 days for placebo. There was no significant difference between the rabeprazole groups.

INDICATIONS

PARIET 10 is indicated for:

- Symptomatic relief of heartburn and other symptoms of gastro-oesophageal reflux disease

CONTRAINDICATIONS

PARIET 10 is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET 10 does not preclude the presence of gastric malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET 10.

Patients on PARIET 10 should be further reviewed and/or investigated if symptoms persist or recur within 2 weeks of completing the course.

Patients should be referred to their doctor for review if:

- they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- they have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- they are being treated for symptomatic GORD and require PARIET 10 for more than 14 days.
- they have any other significant medical condition.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET 10 is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

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Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

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

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Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

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Following intravenous administration of ^{14}C -labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m^2) resulted in decreases in body weight gain of the pups.

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Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Patients may need to be monitored when these drugs are taken together with PARIET 10.

Effect of rabeprazole sodium on other drugs - theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs - potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxycillin (as single and multiple oral doses).

Taking PARIET 10 with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Rabeprazole was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the rabeprazole treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of rabeprazole.

The adverse events, which may or may not be causally related to rabeprazole, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with rabeprazole. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including

thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Adults 18 years of age and over:

The recommended dose is one tablet per day to be taken at the same time each day (to facilitate treatment compliance) for at least 7 days and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with PARIET 10, patients should be referred to their doctor. PARIET 10 tablets should not be chewed or crushed, but should be swallowed whole. PARIET 10 tablets were taken with or without food in the pivotal clinical trials.

Use in Children under 18 years of age

PARIET 10 is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET 10 tablets are pink, biconvex tablets, marked with “ε 241” in black ink on one side. Supplied in blister packs of 7 and 14 tablets.

Storage Conditions

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Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

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1-5 Khartoum Rd
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Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 3 – Pharmacist Only Medicine.

DATE OF FIRST INCLUSION IN THE ARTG

01 April 2010

DATE OF MOST RECENT AMENDMENT

XXXXXX

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PARIET 10[®] Tablets

PRODUCT INFORMATION

FOI 26-2974 - Document 20

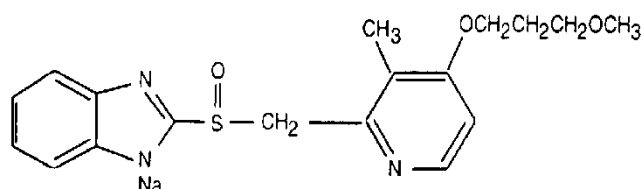
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:

 $C_{18}H_{20}N_3NaO_3S$

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET 10 is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole).

PARIET 10 tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax, iron oxide red CI 77491 and Edible Ink Gray F6.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months' duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years' duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET 10 tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ¹⁴C-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 the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $AUC_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

CLINICAL TRIALS

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

The efficacy of rabeprazole 10 mg or 20 mg daily versus placebo was assessed in a randomised, double blind, parallel group study (n=199) over a four week interval in subjects with moderately severe gastro-oesophageal reflux disease and grade 0 or 1 oesophagitis at endoscopy. The primary efficacy variable was defined as the time in days for subjects to achieve their first 24 hour interval without heartburn. Results showed that the average times were 6.541 +/- 0.923 days for rabeprazole 10 mg, 10 +/- 1.258 days for rabeprazole 20 mg and 16.347 +/- 1.105 days for placebo. There was no significant difference between the rabeprazole groups.

INDICATIONS

PARIET 10 is indicated for:

- Symptomatic relief of heartburn and other symptoms of gastro-oesophageal reflux disease

CONTRAINDICATIONS

PARIET 10 is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET 10 does not preclude the presence of gastric malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET 10.

Patients on PARIET 10 should be further reviewed and/or investigated if symptoms persist or recur within 2 weeks of completing the course.

Patients should be referred to their doctor for review if:

- they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- they have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- they are being treated for symptomatic GORD and require PARIET 10 for more than 14 days.
- they have any other significant medical condition.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET 10 is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Patients should be referred to their doctor for review if they have severe hepatic impairment (eg. cirrhosis).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at 20 mg/day.

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively, and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs - demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET 10:

Clonidogrel: Clonidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clonidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clonidogrel should be discouraged.

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir. Co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET 10 should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Effect of rabeprazole sodium on other drugs - theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs - potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET 10 with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Rabeprazole was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the rabeprazole treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of rabeprazole.

The adverse events, which may or may not be causally related to rabeprazole, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

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Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with rabeprazole. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesaemia has also been reported rarely.

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There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) (see **PRECAUTIONS**).

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Use in Children under 18 years of age

PARIET 10 is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

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POISON SCHEDULE OF THE MEDICINE

Schedule 3 – Pharmacist Only Medicine.

DATE OF FIRST INCLUSION IN THE ARTG

01 April 2010

DATE OF MOST RECENT AMENDMENT

<To be updated upon approval>

® PARIET is a trademark of Eisai Ltd.



EXP:

PARIET 10[®] Tablets

PRODUCT INFORMATION

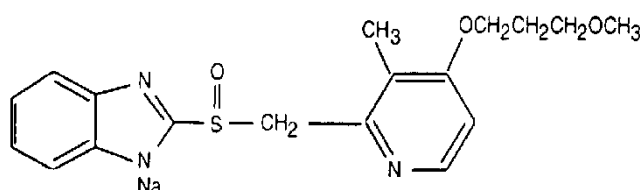
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

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The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET 10 is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole).

PARIET 10 tablets contain the inactive ingredients mannitol, magnesium oxide, hydroxypropylcellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax, iron oxide red CI 77491 and Edible Ink Gray F6.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months' duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years' duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET 10 tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

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In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $AUC_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

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Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

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Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) ($p < 0.00001$).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group ($p = 0.0011$). Treatment failure was associated with an increased antacid consumption.

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INDICATIONS

PARIET 10 is indicated for:

- Symptomatic relief of heartburn and other symptoms of gastro-oesophageal reflux disease

CONTRAINDICATIONS

PARIET 10 is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET 10 does not preclude the presence of gastric malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET 10.

Patients on PARIET 10 should be further reviewed and/or investigated if symptoms persist or recur within 2 weeks of completing the course.

Patients should be referred to their doctor for review if:

- they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- they have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- they are being treated for symptomatic GORD and require PARIET 10 for more than 14 days.
- they have any other significant medical condition.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET 10 is first initiated in patients with severe hepatic dysfunction (see **DOSE & ADMINISTRATION**).

Patients should be referred to their doctor for review if they have severe hepatic impairment (eg. cirrhosis).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at 20 mg/day.

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively, and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interference with Laboratory Tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. CgA increases due to decreased gastric acidity. To avoid this interference, proton pump inhibitors should be stopped 14 days before CgA measurements

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs - demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET 10:

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir. Co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET 10 should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Effect of rabeprazole sodium on other drugs - theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs - potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET 10 with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Rabeprazole was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the rabeprazole treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of rabeprazole.

The adverse events, which may or may not be causally related to rabeprazole, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.
<i>Other:</i>	depression.

Post-Marketing Experience

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with rabeprazole. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Adults 18 years of age and over:

The recommended dose is one tablet per day to be taken at the same time each day (to facilitate treatment compliance) for at least 7 days and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with PARIET 10, patients should be referred to their doctor. PARIET 10 tablets should not be chewed or crushed, but should be swallowed whole. PARIET 10 tablets were taken with or without food in the pivotal clinical trials.

Use in Children under 18 years of age

PARIET 10 is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Hepatic or Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **PRECAUTIONS**).

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET 10 tablets are pink, biconvex tablets, marked with “ε 241” in black ink on one side. Supplied in blister packs of 7 and 14 tablets.

Storage Conditions

PARIET 10 tablets should be stored below 25°C. Do not refrigerate or freeze.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 3 – Pharmacist Only Medicine.

DATE OF FIRST INCLUSION IN THE ARTG

01 April 2010

DATE OF MOST RECENT AMENDMENT

® PARIET is a trademark of Eisai Ltd.

PARIET 10[®] Tablets

PRODUCT INFORMATION

FOI 26-2974 - Document 23

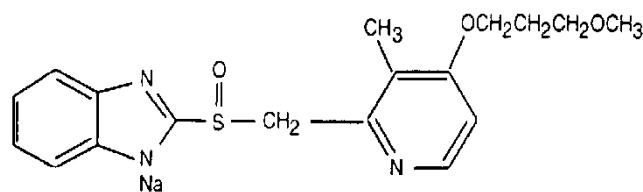
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:

C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

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INDICATIONS

PARIET 10 is indicated for:

- Symptomatic relief of heartburn and other symptoms of gastro-oesophageal reflux disease

CONTRAINDICATIONS

PARIET 10 is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET 10 does not preclude the presence of gastric malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET 10.

Patients on PARIET 10 should be further reviewed and/or investigated if symptoms persist or recur within 2 weeks of completing the course.

Patients should be referred to their doctor for review if:

- they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- they have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- they are being treated for symptomatic GORD and require PARIET 10 for more than 14 days.
- they have any other significant medical condition.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET 10 is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Patients should be referred to their doctor for review if they have severe hepatic impairment (eg. cirrhosis).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Fundic gland polyps

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

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at 20 mg/day.

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively, and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interference with Laboratory Tests

PPI-induced decreases in gastric acidity may lead to increases in serum chromogranin A (CgA) levels, which may lead to erroneous interpretations of laboratory results in investigations for neuroendocrine tumors. To avoid this interference, temporarily stop TRADENAME treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs - demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET 10:

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir. Co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET 10 should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Effect of rabeprazole sodium on other drugs - theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs - potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET 10 with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of rabeprazole based on the comprehensive assessment of the available adverse event information. A causal relationship with rabeprazole cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trials

Rabeprazole was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the rabeprazole treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of rabeprazole.

The adverse events, which may or may not be causally related to rabeprazole, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

Gastrointestinal: dyspepsia, eructation, dry mouth.

Respiratory: sinusitis, bronchitis.

Musculoskeletal: arthralgia, leg cramps.

Urinary: urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

Gastrointestinal: anorexia, gastritis, weight gain, stomatitis.

Skin: pruritis, sweating.

Special Senses: vision or taste disturbances.

Haematologic: leucocytosis.

Other: depression.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience.

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with rabeprazole. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION**Adults 18 years of age and over:**

The recommended dose is one tablet per day to be taken at the same time each day (to facilitate treatment compliance) for at least 7 days and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with PARIET 10, patients should be referred to their doctor. PARIET 10 tablets should not be chewed or crushed, but should be swallowed whole. PARIET 10 tablets were taken with or without food in the pivotal clinical trials.

Use in Children under 18 years of age

PARIET 10 is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal impairment.

Use in Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see PRECAUTIONS).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET 10 tablets are pink, biconvex tablets, marked with “ε 241” in black ink on one side. Supplied in blister packs of 7 and 14 tablets.

Storage Conditions

PARIET 10 tablets should be stored below 25°C. Do not refrigerate.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 3 – Pharmacist Only Medicine.

DATE OF FIRST INCLUSION IN THE ARTG

01 April 2010

DATE OF MOST RECENT AMENDMENT

® PARIET is a trademark of Eisai Ltd.

PARIET 10[®] Tablets

PRODUCT INFORMATION

FOI 26-2974 - Document 24

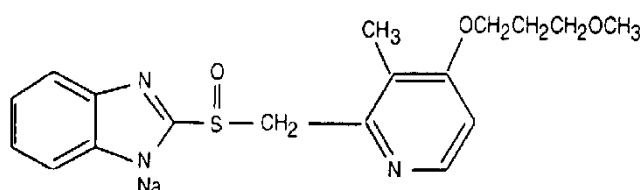
NAME OF THE DRUG

Rabeprazole sodium

DESCRIPTION

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors. Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers. It has the following structural formula:



$C_{18}H_{20}N_3NaO_3S$

MW: 381.43

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

PARIET 10 is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole).

PARIET 10 tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax, iron oxide red and Edible Ink Gray F6.

PHARMACOLOGY

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H^+/K^+ -ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Pharmacodynamics

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H^+/K^+ -ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months' duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years' duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **Carcinogenicity, Mutagenicity and Impairment of Fertility**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Pharmacokinetics

Absorption: PARIET 10 tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Elimination and Excretion: Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Special populations

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC₀₋₂₄ was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, AUC_{0-∞} and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **DOSAGE AND ADMINISTRATION** section for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

CLINICAL TRIALS

Symptomatic Gastro-Oesophageal Reflux Disease (GORD): On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) (p<0.00001).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group (p=0.0011). Treatment failure was associated with an increased antacid consumption.

The efficacy of rabeprazole 10 mg or 20 mg daily versus placebo was assessed in a randomised, double blind, parallel group study (n=199) over a four week interval in subjects with moderately severe gastro-oesophageal reflux disease and grade 0 or 1 oesophagitis at endoscopy. The primary efficacy variable was defined as the time in days for subjects to achieve their first 24 hour interval without heartburn. Results showed that the average times were 6.541 +/- 0.923 days for rabeprazole 10 mg, 10 +/- 1.258 days for rabeprazole 20 mg and 16.347 +/- 1.105 days for placebo. There was no significant difference between the rabeprazole groups.

INDICATIONS

PARIET 10 is indicated for:

- Symptomatic relief of heartburn and other symptoms of gastro-oesophageal reflux disease

CONTRAINDICATIONS

PARIET 10 is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

PRECAUTIONS

Symptomatic response to therapy with PARIET 10 does not preclude the presence of gastric malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET 10.

Patients on PARIET 10 should be further reviewed and/or investigated if symptoms persist or recur within 2 weeks of completing the course.

Patients should be referred to their doctor for review if:

- they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- they have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- they are being treated for symptomatic GORD and require PARIET 10 for more than 14 days.
- they have any other significant medical condition.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Use in Patients with Hepatic Impairment.

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET 10 is first initiated in patients with severe hepatic dysfunction (see **DOSAGE & ADMINISTRATION**).

Patients should be referred to their doctor for review if they have severe hepatic impairment (eg. cirrhosis).

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **ADVERSE REACTIONS**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Fundic gland polyps

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

Carcinogenicity, Mutagenicity and Impairment of Fertility

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day.

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg.hr/mL which is 1.6 times the human exposure at 20 mg/day.

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg.hr/mL which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg.hr/mL (0.2 times the human exposure at 20 mg/day).

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-)). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in Pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively, and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Interference with Laboratory Tests

PPI-induced decreases in gastric acidity may lead to increases in serum chromogranin A (CgA) levels, which may lead to erroneous interpretations of laboratory results in investigations for neuroendocrine tumors. To avoid this interference, temporarily stop TRADENAME treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

INTERACTIONS WITH OTHER MEDICINES

Effect of rabeprazole sodium on other drugs - demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET 10:

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir. Co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET 10 should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Effect of rabeprazole sodium on other drugs - theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs - potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxicillin (as single and multiple oral doses).

Taking PARIET 10 with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

ADVERSE REACTIONS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of rabeprazole based on the comprehensive assessment of the available adverse event information. A causal relationship with rabeprazole cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trials

Rabeprazole was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the rabeprazole treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of rabeprazole.

The adverse events, which may or may not be causally related to rabeprazole, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

Nervous System:	headache, dizziness.
Gastrointestinal:	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
Respiratory:	rhinitis, pharyngitis, cough.
Musculoskeletal:	non-specific pain, back pain, myalgia.
Skin:	rash.
Other:	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

Gastrointestinal: dyspepsia, eructation, dry mouth.

Respiratory: sinusitis, bronchitis.

Musculoskeletal: arthralgia, leg cramps.

Urinary: urinary tract infection.

Other: fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

Gastrointestinal: anorexia, gastritis, weight gain, stomatitis.

Skin: pruritis, sweating.

Special Senses: vision or taste disturbances.

Haematologic: leucocytosis.

Other: depression.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience.

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with rabeprazole. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see **PRECAUTIONS**).

Gastrointestinal disorders

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

DOSAGE AND ADMINISTRATION**Adults 18 years of age and over:**

The recommended dose is one tablet per day to be taken at the same time each day (to facilitate treatment compliance) for at least 7 days and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with PARIET 10, patients should be referred to their doctor. PARIET 10 tablets should not be chewed or crushed, but should be swallowed whole. PARIET 10 tablets were taken with or without food in the pivotal clinical trials.

Use in Children under 18 years of age

PARIET 10 is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal impairment.

Use in Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see PRECAUTIONS).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with hepatic impairment.

OVERDOSAGE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

PRESENTATION AND STORAGE CONDITIONS

PARIET 10 tablets are pink, biconvex tablets, marked with "E 241" in black ink on one side. Supplied in blister packs of 7 and 14 tablets.

Storage Conditions

PARIET 10 tablets should be stored below 25°C. Do not refrigerate.

Tablets are presented in an aluminium/aluminium blister.

NAME AND ADDRESS OF THE SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 3 – Pharmacist Only Medicine.

DATE OF FIRST INCLUSION IN THE ARTG

01 April 2010

DATE OF MOST RECENT AMENDMENT

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PARIET 10[®]

RABEPRAZOLE SODIUM

AUSTRALIAN PRODUCT INFORMATION

1 NAME OF THE MEDICINE

Rabeprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PARIET 10 is available as enteric coated tablets containing 10 mg rabeprazole sodium (equivalent to 9.42 mg rabeprazole).

For the full list of excipients, see **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

PARIET 10 tablets are pink, biconvex tablets, marked with "ε 241" in black ink on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PARIET 10 is indicated for:

- Symptomatic relief of heartburn and other symptoms of gastro-oesophageal reflux disease

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults 18 years of age and over:

The recommended dose is one tablet per day to be taken at the same time each day (to facilitate treatment compliance) for at least 7 days and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with PARIET 10, patients should be referred to their doctor. PARIET 10 tablets should not be chewed or crushed, but should be swallowed whole. PARIET 10 tablets were taken with or without food in the pivotal clinical trials.

Use in Children under 18 years of age

PARIET 10 is not recommended for use in children as there is no experience of its use in this group.

Use in Elderly Patients

No dosage adjustment is necessary in elderly patients.

Use in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with renal impairment.

Use in Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients. Caution should be exercised in patients with severe hepatic impairment (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

There are no data on the use of rabeprazole in combination with antibiotic regimens in patients with hepatic impairment.

4.3 CONTRAINDICATIONS

PARIET 10 is contraindicated in patients with known hypersensitivity to rabeprazole sodium, proton pump inhibitors, or any ingredient of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic response to therapy with PARIET 10 does not preclude the presence of gastric malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with PARIET 10.

Patients on PARIET 10 should be further reviewed and/or investigated if symptoms persist or recur within 2 weeks of completing the course.

Patients should be referred to their doctor for review if:

- they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- they have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- they are being treated for symptomatic GORD and require PARIET 10 for more than 14 days.
- they have any other significant medical condition.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton-pump inhibitors (PPIs) including rabeprazole sodium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 then periodically while treatment continues (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Fractures

Observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).

Concomitant use of Rabeprazole with Methotrexate

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

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

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

Fundic gland polyps

As with other PPIs, long-term use of rabeprazole is associated with an increased risk of fundic gland polyps (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Post-marketing data**). Most fundic gland polyps are asymptomatic. Patients with large or ulcerated polyps may be at risk of gastrointestinal bleeding or small intestinal blockage. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Use in hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment. While no evidence of significant drug related safety problems was observed in patients with hepatic impairment, it is advised to exercise caution when treatment with PARIET 10 is first initiated in patients with severe hepatic dysfunction (see **4.2 DOSE AND METHOD OF ADMINISTRATION**). Patients should be referred to their doctor for review if they have severe hepatic impairment (eg. cirrhosis).

Use in renal impairment

No data available

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

PPI-induced decreases in gastric acidity may lead to increases in serum chromogranin A (CgA) levels, which may lead to erroneous interpretations of laboratory results in investigations for neuroendocrine tumors. To avoid this interference, temporarily stop TRADENAME treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of rabeprazole sodium on other drugs - demonstrated interactions

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

Patients may need to be monitored when the following drugs are taken together with PARIET 10:

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged.

Cyclosporin: *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days dosing with 20 mg rabeprazole. Although *in vitro* studies may not always be predictive of an *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

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

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly.

Ketoconazole: A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly.

Atazanavir. Co-administration of atazanavir with other proton pump inhibitors resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore, PARIET 10 should not be co-administered with atazanavir.

Mycophenolate mofetil: co-administration of proton-pump inhibitors with mycophenolate mofetil in healthy and transplant patients has been reported to reduce the exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate

mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton-pump inhibitors and mycophenolate mofetil. Use rabeprazole sodium with caution in transplant patients receiving mycophenolate mofetil.

Effect of rabeprazole sodium on other drugs - theoretical interactions

Rabeprazole sodium 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 sodium.

Effect of rabeprazole sodium on other drugs - potential interactions that have been excluded

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system. These studies included the drugs warfarin and theophylline (as single oral doses), phenytoin (as a single intravenous dose with supplemental oral dosing), diazepam (as a single intravenous dose) and amoxycillin (as single and multiple oral doses).

Taking PARIET 10 with antacids produces no clinically relevant changes in plasma rabeprazole sodium concentrations.

Plasma concentrations of rabeprazole and the active metabolite of clarithromycin are increased by 24% and 50% respectively during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg.hr/mL, about 10 times the human exposure at 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

Use in pregnancy

Category B1.

Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg.hr/mL, about 13 or 6.5 times the human exposure at 20 mg/day and 40mg/day respectively, and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg.hr/mL, about 8 or 4 times the human exposure at 20 mg/day and 40mg/day respectively) and have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole. There are no adequate and well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

Following intravenous administration of ¹⁴C-labelled rabeprazole to lactating rats, radioactivity in milk reached levels that were about 2- to 7-fold higher than levels in the blood. Administration of rabeprazole to rats in gestation and during lactation at doses of 400 mg/kg/day (about 195- or 85-times a 20mg or 40mg human dose based on mg/m²) resulted in decreases in body weight gain of the pups.

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Since many drugs are excreted in milk and because of the

potential for adverse reactions to nursing infants from rabeprazole sodium, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of rabeprazole based on the comprehensive assessment of the available adverse event information. A causal relationship with rabeprazole cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trials

Rabeprazole was generally well tolerated during clinical trials. The observed side effects have generally been mild or moderate and transient in nature. In the majority of cases, the incidence of the adverse events in the rabeprazole treatment group was equal to or less than that observed in the placebo control treatment group.

Only headaches, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth have been associated with the use of rabeprazole.

The adverse events, which may or may not be causally related to rabeprazole, reported in clinical trials are listed below in descending order of frequency.

Common ($\geq 1\%$ and $< 10\%$)

<i>Nervous System:</i>	headache, dizziness.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough.
<i>Musculoskeletal:</i>	non-specific pain, back pain, myalgia.
<i>Skin:</i>	rash.
<i>Other:</i>	asthenia, flu-like syndrome, infection, insomnia, chest pain.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

<i>Gastrointestinal:</i>	dyspepsia, eructation, dry mouth.
<i>Respiratory:</i>	sinusitis, bronchitis.
<i>Musculoskeletal:</i>	arthralgia, leg cramps.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	fever, nervousness, somnolence, chills, peripheral oedema.

Rare ($\geq 0.01\%$ and $< 0.1\%$)

<i>Gastrointestinal:</i>	anorexia, gastritis, weight gain, stomatitis.
<i>Skin:</i>	pruritis, sweating.
<i>Special Senses:</i>	vision or taste disturbances.
<i>Haematologic:</i>	leucocytosis.

Other: depression.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience.

Erythema and rarely bullous reactions, urticarial skin eruptions and acute systemic allergic reactions, for example facial swelling, hypotension and dyspnoea have been reported in patients treated with rabeprazole. These usually resolved after discontinuation of therapy.

Erythema multiforme, interstitial nephritis, gynaecomastia, myalgia and potential allergic reactions including anaphylactic reactions have been reported rarely. Blood dyscrasia including thrombocytopenia, neutropenia, leukopenia, pancytopenia, agranulocytosis and bicytopenia have been reported rarely. Hypomagnesemia has also been reported rarely.

There have also been reports of increased hepatic enzymes and serious hepatic dysfunction such as hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and bullous rashes including subacute cutaneous lupus erythematosus.

There have been post-marketing reports of bone fractures and post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Gastrointestinal disorders

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be used.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Rabeprazole sodium is a substituted benzimidazole and belongs to the class of proton pump inhibitors.

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell thereby

blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa.

Mechanism of Action

Anti-Secretory Activity: Oral administration of a 20 mg dose of PARIET provides rapid and effective reduction of gastric acid secretion. The onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding of rabeprazole sodium to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Serum Gastrin Effects: In clinical studies, patients were treated once daily with 10 or 20 mg rabeprazole sodium for up to 12 months' duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. In a maintenance study, which was subsequently extended up to 5 years' duration, serum gastrin levels were only modestly raised in most patients.

Enterochromaffin-Like (ECL) Cell Effects: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially females (see **5.3 PRECLINICAL SAFETY DATA**).

In over 400 patients treated with PARIET (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Clinical trials

Symptomatic Gastro-Oesophageal Reflux Disease (GORD):

On-demand treatment was assessed in a European multicentre, double-blind placebo-controlled randomised withdrawal study (n=418) in endoscopically negative patients.

Following an acute open-label phase, patients were randomised to receive rabeprazole 10 mg or placebo taken once daily, when required, over a six month period. Efficacy of rabeprazole 10 mg on-demand, in patients with complete heartburn relief at baseline was primarily evaluated by the unwillingness to continue the trial because of inadequate heartburn control. Overall, the proportion of patients discontinuing due to inadequate heartburn control was significantly higher for placebo (20%) compared to rabeprazole (6%) (p<0.00001).

Patients were instructed to take study drug until they had experienced a full 24 hours free of heartburn, most patients in the rabeprazole group had maximum episode duration of 4 days or less. In addition, antacid use was about 2-fold higher in the placebo group than in the rabeprazole group (p=0.0011). Treatment failure was associated with an increased antacid consumption.

The efficacy of rabeprazole 10 mg or 20 mg daily versus placebo was assessed in a randomised, double blind, parallel group study (n=199) over a four week interval in subjects

with moderately severe gastro-oesophageal reflux disease and grade 0 or 1 oesophagitis at endoscopy. The primary efficacy variable was defined as the time in days for subjects to achieve their first 24 hour interval without heartburn. Results showed that the average times were 6.541 +/- 0.923 days for rabeprazole 10 mg, 10 +/- 1.258 days for rabeprazole 20 mg and 16.347 +/- 1.105 days for placebo. There was no significant difference between the rabeprazole groups.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

PARIET 10 tablets are enteric coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach intact. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole sodium and AUC are linear over the dose range of 10 mg to 40 mg.

Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52%, largely due to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 mL/min.

Distribution

Rabeprazole sodium is approximately 97% bound to human plasma proteins. After intravenous administration the volume of distribution is 0.34 L/kg.

Metabolism

Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **4.5 INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTIONS**). In humans, the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but its presence in plasma is minimal.

Excretion

Following a single 20 mg ^{14}C -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This suggests low biliary excretion of the metabolites; with bio-transformation and urinary excretion of water soluble metabolites as the primary route of elimination.

Special populations

Renal Disease: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $AUC_{0-\infty}$ and C_{MAX} values increased approximately 30% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the **4.2 DOSE AND METHOD OF ADMINISTRATION** for information on dosage adjustments in patients with hepatic impairment.

Geriatrics: Elimination of rabeprazole sodium was decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled and the C_{max} increased by 60% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

5.3 PRECLINICAL SAFETY DATA

Note: In the following section, the relative exposure levels in animals have been calculated using a human dose of 20mg/day.

Genotoxicity

Rabeprazole was positive in assays for gene mutations (the AMES test, forward gene mutation tests in Chinese hamster ovary cells (CHO/HGPRT) and mouse lymphoma cells (L5178Y/TK+/-). Its demethylated-metabolite was also positive in the AMES test. Rabeprazole was negative in assays for chromosomal damage (the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test), and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Carcinogenicity

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumour occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is 1.6 times the human exposure at 20 mg/day.

In a 104-week carcinogenicity study in SD rats, males were treated with oral doses of 5, 15, 30 and 60mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumours in female rats at all doses. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is about 0.1 times the human exposure at 20 mg/day. In male rats, no treatment-related tumours were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (0.2 times the human exposure at 20 mg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

PARIET 10 tablets contain the inactive ingredients mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax, iron oxide red and Edible Ink Gray F6.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. (see **4.5 INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTIONS**)

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

PARIET 10 tablets should be stored below 25°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

Pariet 10 tablets are presented in blister packs of 7 and 14 tablets. Tablets are presented in an aluminium/aluminium blister.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

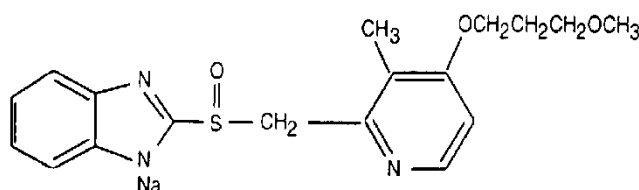
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name for rabeprazole sodium is (±) 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulphonyl]-1H-benzimidazole sodium. Rabeprazole has one chiral centre and is a racemate of two enantiomers.

Its solubility in water is pH dependent, being very soluble in water at pH 9 to 11, and only slightly soluble in water at pH 8. It is very soluble in methanol, freely soluble in dichloromethane and practically insoluble in hexane.

Chemical structure



C₁₈H₂₀N₃NaO₃S

MW: 381.43

CAS number

CAS-117976-89-3 (rabeprazole)

CAS-117976-90-6 (rabeprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 – Pharmacist Only Medicine.

8 SPONSOR

Janssen-Cilag Pty Ltd,
1-5 Khartoum Road,
Macquarie Park NSW 2113
Telephone: 1800 226 334

9 DATE OF FIRST APPROVAL

01 April 2010

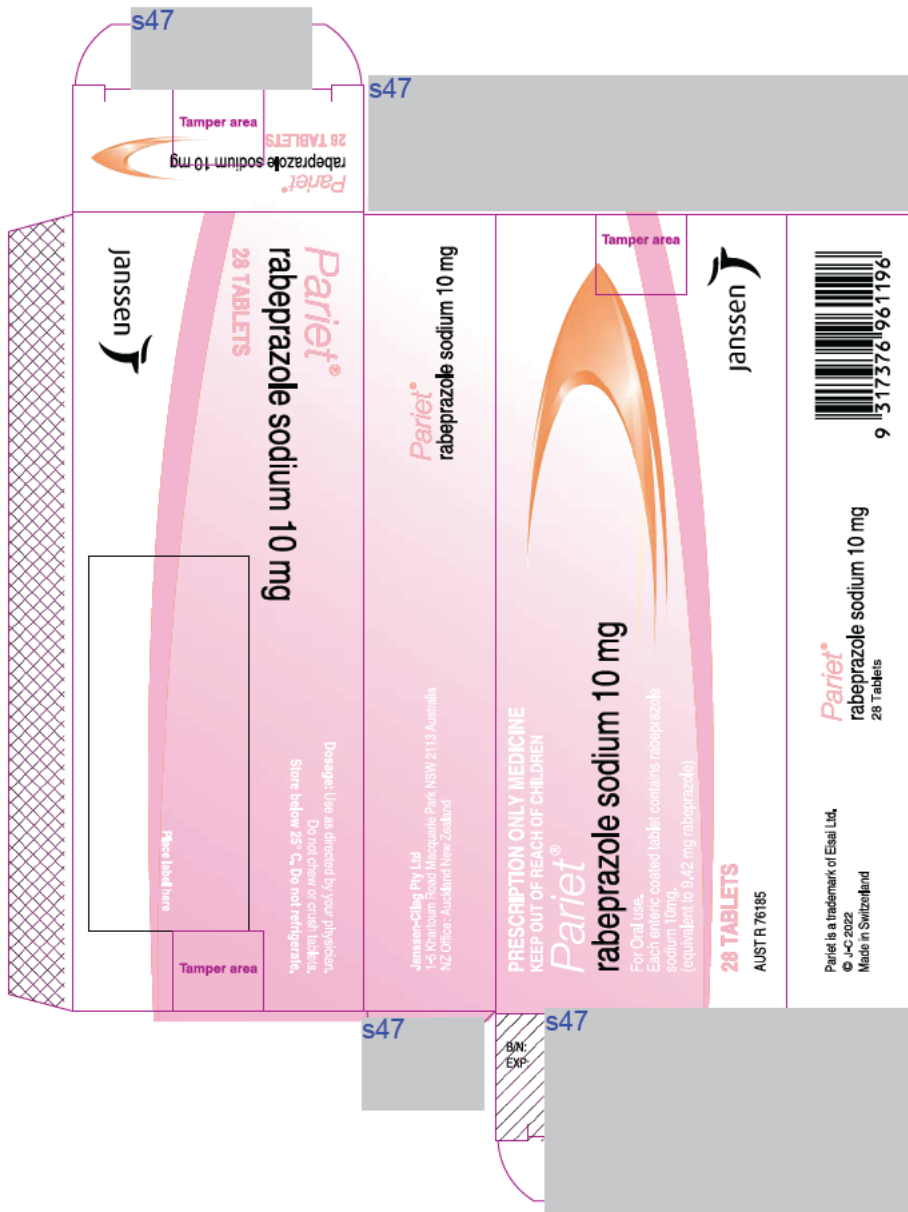
10 DATE OF REVISION

TBD

® PARIET is a trademark of Eisai Ltd.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformat



s47

s47

Pariet®
rabeprazole sodium 10 mg
28 TABLETS

janssen

Pariet®
rabeprazole sodium 10 mg
28 TABLETS

janssen

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EXP.
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s47

10mg

JANSSEN-CILAG

Pariet® 10mg

rabeprazole sodium 10 mg

28 TABLETS

Dosage: Use as directed by your physician.
Do not chew or crush tablets.
Store below 25° C.

10 mg

Janssen-Cilag Pty Ltd
1-5 Kildrum Road North Ryde NSW 2113 Australia
NZ Office: Auckland New Zealand

**PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN**

Pariet® 10mg

Each tablet contains rabeprazole sodium 10 mg
(equivalent to 9.42 mg rabeprazole)

28 TABLETS
AUST R 76185

JANSSEN-CILAG



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© J-C 2008

s47

Pariet
rabeprazole sodium 10 mg
28 TABLETS

10mg

s47

PARIET[®] Tablets

Rabeprazole sodium

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about PARIET tablets. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking PARIET against the benefits this medicine is expected to have for you.

If you have any concerns about using PARIET ask your doctor or pharmacist.

Keep this leaflet with your medicine.

You may need to read it again.

What PARIET is used for

The name of your medicine is PARIET. It contains the active ingredient rabeprazole sodium.

PARIET belongs to a group of medicines called proton pump inhibitors (PPIs). PARIET works by decreasing the amount of acid the stomach makes, to give relief from the symptoms and allow healing to take place. Your food will still be digested in the same way.

Gastro-oesophageal reflux disease:

PARIET is used to treat gastro-oesophageal reflux disease (GORD), commonly known as 'reflux'. This can be caused by food and acid from the stomach flowing the wrong way (reflux) back up the food pipe, also known as the oesophagus.

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn. PARIET is also used to help stop gastro-oesophageal reflux disease from coming back or relapsing.

Peptic Ulcers:

PARIET is used to treat peptic ulcers. Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum, which is the tube leading out of the stomach.

These ulcers can be caused by too much acid being made in the stomach.

Most people who have a peptic ulcer also have bacteria called *Helicobacter pylori* in their stomach. Your doctor may also prescribe a course of antibiotics (clarithromycin and amoxycillin) for you. When PARIET is taken with antibiotics, the combination therapy will kill the *Helicobacter pylori* and let your ulcer heal.

Chronic Gastritis:

The presence of the bacteria *Helicobacter pylori* may cause the stomach to become inflamed, resulting in pain, nausea and vomiting; all of which are signs of chronic gastritis.

When PARIET tablets are taken with antibiotics, they will help kill *Helicobacter pylori* and allow the stomach to heal.

Your doctor may have prescribed PARIET for another reason. Ask your doctor if you have any questions about why PARIET has been prescribed for you.

PARIET is only available with a doctor's prescription.

Before you take PARIET

When you must not take it:

Do not take PARIET if you have an allergy (hypersensitivity) to:

- rabeprazole sodium
- any of the ingredients listed at the end of this leaflet.
- other proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole).

Symptoms of an allergic (hypersensitive) reaction may include:

- rash, itching or hives on the skin
- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body

Do not take PARIET if:

- the packaging is torn or shows signs of tampering.
- the expiry date (month and year) printed on the pack has passed. If you take PARIET after the expiry date it may not work.

PARIET should not be given to children under 18 years of age. Safety and effectiveness of PARIET in children has not been established.

Before you start to take it:

You must tell your doctor if:

- you are pregnant or intend to become pregnant.

- you are breast-feeding or intend to breast-feed. It is not known if PARIET passes into breast milk.
- you have now, or have had in the past, liver problems.

Taking other medicines:

Tell your doctor or pharmacist if you are taking any other medicines, including medicines you can buy without a prescription from a pharmacy, supermarket or health food shop.

Do not take PARIET and tell your doctor or pharmacist if you are taking any of the following:

- atazanavir, a medicine used (with other antiretrovirals) to treat HIV-1 infection.
- clopidogrel, an antiplatelet medicine.

You should not take PARIET while taking these medicines.

Also tell your doctor or pharmacist if you are taking any of the following:

- cyclosporin, a medicine used to treat several conditions including prevention of graft rejection following kidney, liver or heart transplantation; severe, active rheumatoid arthritis; severe skin diseases; kidney disease where other treatments have failed.
- methotrexate, a medicine used to treat some kinds of cancer. It is also used to treat psoriasis (skin disease) and rheumatoid arthritis.
- digoxin, a medicine used to treat heart problems.
- ketoconazole, a medicine used to treat fungal infections.
- mycophenolate mofetil, a medicine used to prevent organ rejection following kidney, liver or heart transplants.
- clarithromycin, a medicine used to treat infections.

These medicines may be affected by PARIET or may affect how well PARIET works. Your doctor or

pharmacist can tell you what to do if you are taking any other medicines.

If you have not told your doctor or pharmacist about any of the above, tell them before you start taking PARIET.

Your doctor will advise you whether or not to take PARIET or if you need to have your dose adjusted.

How to take PARIET

Follow the directions given to you by your doctor and pharmacist carefully. They may differ from the information contained in this leaflet.

How much to take:

Adults

The usual dose is one tablet, to be taken once daily, at the same time each day.

The dose of PARIET tablets is usually 20 mg, but may vary from 10 mg to 40 mg per day depending on what condition you are being treated for and how severe it is.

For treating *Helicobacter pylori* infections in combination with antibiotics (clarithromycin and amoxicillin), the usual dose is one 20mg tablet twice daily, morning and evening, for 7 days.

Children

PARIET should not be given to children under 18 years of age. Safety and effectiveness of PARIET in children has not been established.

How to take it:

- PARIET should be swallowed whole, with a glass of water or other liquid.
- Do NOT crush or chew the tablets. They have a special coating, which protects them from the acid in your stomach. If the coating is broken by chewing, the tablets may not work.

- It does not matter if you take PARIET with food or on an empty stomach.

Ask your doctor or pharmacist for help if you do not understand the instructions provided with this medicine.

If you forget to take it:

If you forget to take your tablet, take it as soon as you remember and then continue to take it as you would normally.

However, if it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you are not sure what to do, check with your doctor or pharmacist.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you have taken too much (overdose):

If you think that you, or anyone else, may have taken too much PARIET, immediately telephone your doctor or the Poisons Information Centre (telephone 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

While you are using PARIET

Things you must do:

- Use PARIET exactly as your doctor has prescribed.
- Always swallow PARIET tablets whole.
- Tell your doctor if you become pregnant while you are taking PARIET

Tell your doctor or pharmacist that you are taking PARIET if you are about to start taking a new medicine.

Things you must not do:

- Do not use PARIET to treat any other complaint unless your doctor says to.
- Do not give this medicine to anyone else, even if they have the same symptoms as you.
- Do not crush or chew the tablets.
- Do not give PARIET to children.

Side Effects

PARIET is usually well tolerated but tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking PARIET.

PARIET helps most people with peptic ulcers or reflux disease, but it may have unwanted side effects in a few people.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some side effects.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor if you notice any of the following and they worry you:

- headache
- dizziness
- diarrhoea
- nausea
- stomach pain
- wind
- vomiting
- constipation
- runny or blocked nose

- sore throat and discomfort when swallowing
- cough
- pain (including back, chest or joint pain)
- muscle weakness, physical weakness or lack of energy
- rash or itchy rash accompanied by skin eruptions or blisters
- flu-like symptoms
- sleeplessness (insomnia)
- indigestion
- belching
- dry mouth
- leg cramps
- swelling of the arms or legs
- nervousness
- sleepiness (somnolence)
- loss of appetite for food (anorexia)
- weight gain
- sweating

These side effects are usually mild.

Tell your doctor immediately if you notice any of the following:

- painful and/or frequent urination (common symptoms of a urinary tract infection)
- vision or taste disturbance
- depression
- feeling dizzy, faint, lightheaded or weak (hypotension)
- shortness of breath
- signs of frequent infections such as fever, chills, sore throat or mouth ulcers.

These are serious side effects. You may need urgent medical attention. Serious side effects are rare.

Tell your doctor immediately and do not take your next dose of PARIET if you experience:

- signs of allergy such as skin rash, reddening, blisters or itching, swelling of the face, lips or other parts of the body, shortness of breath or wheezing.

If you experience symptoms such as severe (watery or bloody) diarrhoea, fever, abdominal pain or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation).

Other problems are more likely to arise from the ulcer itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

Under rare circumstances supervised by the doctor, proton pump inhibitors (PPIs) might be used for long periods of time.

Low magnesium can occur in some people who take a proton pump inhibitor. Symptoms of low magnesium can include: seizures, dizziness, spasms, cramps or muscle weakness.

People who take proton pump inhibitor medicines at high doses for a long period of time (1 year or longer) may have an increased risk of fractures of the hip, wrist, or spine.

Proton pump inhibitors may reduce the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor or pharmacist about the possibility of vitamin B-12 deficiency if you have been taking a proton pump inhibitor for a long time (i.e. more than 3 years).

Other side effects not listed above may also occur in some people. Tell your doctor if you notice anything making you feel unwell when you are taking, or soon after you have finished taking PARIET.

Ask your doctor or pharmacist if you do not understand anything in this list.

After using PARIET

Storage

PARIET tablets are packaged in a double-sided aluminium blister strip.

Do not take PARIET tablets out of the blister pack until it is time to take them. If you take them out of the blister they may not keep well.

Keep PARIET tablets in a cool dry place where the temperature is below 25°C. Do not keep PARIET in the refrigerator or freezer.

Do not store PARIET, or any other medicine, in the bathroom or near a sink. Do not leave medicines in the car or on window sills. Heat and dampness can destroy some medicines.

Keep your medicines where children cannot reach them. A locked cupboard at least one-and-a-half metres (1.5 m) above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking PARIET tablets, or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets that are left over.

Product Description

What PARIET tablets look like:

PARIET 10 mg tablets are pink and have "E241" in black ink on one side.

PARIET 20 mg tablets are pale yellow, and have "E243" in red ink on one side.

PARIET 10 mg tablets are supplied in blister packs of 7, 28 and 30 tablets.

PARIET 20 mg tablets are supplied in blister packs of 7, 28 and 30 tablets

Ingredients

Each PARIET tablet contains 10 mg or 20 mg of rabeprazole sodium as the active ingredient.

Each tablet also contains the following other ingredients:

- mannitol, magnesium oxide, hyprolose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax.
- the 20 mg tablets also contain iron oxide yellow (E172) and are printed with red ink (Edible Ink Red A1).
- the 10 mg tablets contain iron oxide red (E172) and are printed with gray ink (Edible Ink Gray F6).

The tablets do not contain lactose or gluten.

Sponsor

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Rd

Macquarie Park NSW 2113 Australia

Telephone: Toll Free 1800 226 334

Registration Numbers:

PARIET 10mg AUST R 76185

PARIET 20mg AUST R 76186

This leaflet was prepared in May 2018.

PARIET® is a trademark of Eisai Ltd.

PARIET[®] Tablets

Rabeprazole sodium

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PARIET should not be given to children under 18 years of age. Safety and effectiveness of PARIET in children has not been established.

How to take it:

- PARIET should be swallowed whole, with a glass of water or other liquid.
- Do NOT crush or chew the tablets. They have a special coating, which protects them from the acid in your stomach. If the coating is broken by chewing, the tablets may not work.

- It does not matter if you take PARIET with food or on an empty stomach.

Ask your doctor or pharmacist for help if you do not understand the instructions provided with this medicine.

If you forget to take it:

If you forget to take your tablet, take it as soon as you remember and then continue to take it as you would normally.

However, if it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you are not sure what to do, check with your doctor or pharmacist.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you have taken too much (overdose):

If you think that you, or anyone else, may have taken too much PARIET, immediately telephone your doctor or the Poisons Information Centre (telephone 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

While you are using PARIET

Things you must do:

- Use PARIET exactly as your doctor has prescribed.
- Always swallow PARIET tablets whole.
- Tell your doctor if you become pregnant while you are taking PARIET

Tell your doctor or pharmacist that you are taking PARIET if you are about to start taking a new medicine.

Things you must not do:

- Do not use PARIET to treat any other complaint unless your doctor says to.
- Do not give this medicine to anyone else, even if they have the same symptoms as you.
- Do not crush or chew the tablets.
- Do not give PARIET to children.

Tell your doctor if you need to have a specific blood test (Chromogranin A) while you are taking PARIET 10.

It may affect the results of this test.

Side Effects

PARIET is usually well tolerated but tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking PARIET.

PARIET helps most people with peptic ulcers or reflux disease, but it may have unwanted side effects in a few people.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some side effects.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor if you notice any of the following and they worry you:

- headache
- dizziness
- diarrhoea
- nausea
- stomach pain
- wind

- vomiting
- constipation
- runny or blocked nose
- sore throat and discomfort when swallowing
- cough
- pain (including back, chest or joint pain)
- muscle weakness, physical weakness or lack of energy
- rash or itchy rash accompanied by skin eruptions or blisters
- flu-like symptoms
- sleeplessness (insomnia)
- indigestion
- belching
- dry mouth
- leg cramps
- swelling of the arms or legs
- nervousness
- sleepiness (somnolence)
- loss of appetite for food (anorexia)
- weight gain
- sweating

These side effects are usually mild.

Tell your doctor immediately if you notice any of the following:

- painful and/or frequent urination (common symptoms of a urinary tract infection)
- vision or taste disturbance
- depression
- feeling dizzy, faint, lightheaded or weak (hypotension)
- shortness of breath
- signs of frequent infections such as fever, chills, sore throat or mouth ulcers.

These are serious side effects. You may need urgent medical attention. Serious side effects are rare.

Tell your doctor immediately and do not take your next dose of PARIET if you experience:

- signs of allergy such as skin rash, reddening, blisters or itching,

swelling of the face, lips or other parts of the body, shortness of breath or wheezing.

If you experience symptoms such as severe (watery or bloody) diarrhoea, fever, abdominal pain or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation).

Other problems are more likely to arise from the ulcer itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

Under rare circumstances supervised by the doctor, proton pump inhibitors (PPIs) might be used for long periods of time.

Low magnesium can occur in some people who take a proton pump inhibitor. Symptoms of low magnesium can include: seizures, dizziness, spasms, cramps or muscle weakness.

People who take proton pump inhibitor medicines at high doses for a long period of time (1 year or longer) may have an increased risk of fractures of the hip, wrist, or spine.

Proton pump inhibitors may reduce the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor or pharmacist about the possibility of vitamin B-12 deficiency if you have been taking a proton pump inhibitor for a long time (i.e. more than 3 years).

Other side effects not listed above may also occur in some people. Tell your doctor if you notice anything making you feel unwell when you are taking, or soon after you have finished taking PARIET.

Ask your doctor or pharmacist if you do not understand anything in this list.

After using PARIET

Storage

PARIET tablets are packaged in a double-sided aluminium blister strip.

Do not take PARIET tablets out of the blister pack until it is time to take them. If you take them out of the blister they may not keep well.

Keep PARIET tablets in a cool dry place where the temperature is below 25°C. Do not keep PARIET in the refrigerator or freezer.

Do not store PARIET, or any other medicine, in the bathroom or near a sink. Do not leave medicines in the car or on window sills. Heat and dampness can destroy some medicines.

Keep your medicines where children cannot reach them. A locked cupboard at least one-and-a-half metres (1.5 m) above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking PARIET tablets, or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets that are left over.

Product Description

What PARIET tablets look like:

PARIET 10 mg tablets are pink and have "E241" in black ink on one side.

PARIET 20 mg tablets are pale yellow, and have "E243" in red ink on one side.

PARIET 10 mg tablets are supplied in blister packs of 7, 28 and 30 tablets.

PARIET 20 mg tablets are supplied in blister packs of 7, 28 and 30 tablets

Ingredients

Each PARIET tablet contains 10 mg or 20 mg of rabeprazole sodium as the active ingredient.

Each tablet also contains the following other ingredients:

- mannitol, magnesium oxide, hyprolose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax.
- the 20 mg tablets also contain iron oxide yellow (E172) and are printed with red ink (Edible Ink Red A1).
- the 10 mg tablets contain iron oxide red (E172) and are printed with gray ink (Edible Ink Gray F6).

The tablets do not contain lactose or gluten.

Sponsor

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Rd

Macquarie Park NSW 2113 Australia

Telephone: Toll Free 1800 226 334

Registration Numbers:

PARIET 10mg AUST R 76185

PARIET 20mg AUST R 76186

This leaflet was prepared in July 2018.

PARIET® is a trademark of Eisai Ltd.

PARIET[®] Tablets

Rabeprazole sodium

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about PARIET tablets. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking PARIET against the benefits this medicine is expected to have for you.

If you have any concerns about using PARIET ask your doctor or pharmacist.

Keep this leaflet with your medicine.

You may need to read it again.

What PARIET is used for

The name of your medicine is PARIET. It contains the active ingredient rabeprazole sodium.

PARIET belongs to a group of medicines called proton pump inhibitors (PPIs). PARIET works by decreasing the amount of acid the stomach makes, to give relief from the symptoms and allow healing to take place. Your food will still be digested in the same way.

Gastro-oesophageal reflux disease:

PARIET is used to treat gastro-oesophageal reflux disease (GORD), commonly known as 'reflux'. This can be caused by food and acid from the stomach flowing the wrong way (reflux) back up the food pipe, also known as the oesophagus.

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn. PARIET is also used to help stop gastro-oesophageal reflux disease from coming back or relapsing.

Peptic Ulcers:

PARIET is used to treat peptic ulcers. Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum, which is the tube leading out of the stomach.

These ulcers can be caused by too much acid being made in the stomach.

Most people who have a peptic ulcer also have bacteria called *Helicobacter pylori* in their stomach. Your doctor may also prescribe a course of antibiotics (clarithromycin and amoxycillin) for you. When PARIET is taken with antibiotics, the combination therapy will kill the *Helicobacter pylori* and let your ulcer heal.

Chronic Gastritis:

The presence of the bacteria *Helicobacter pylori* may cause the stomach to become inflamed, resulting in pain, nausea and vomiting; all of which are signs of chronic gastritis.

When PARIET tablets are taken with antibiotics, they will help kill *Helicobacter pylori* and allow the stomach to heal.

Your doctor may have prescribed PARIET for another reason. Ask your doctor if you have any questions about why PARIET has been prescribed for you.

PARIET is only available with a doctor's prescription.

Before you take PARIET

When you must not take it:

Do not take PARIET if you have an allergy (hypersensitivity) to:

- rabeprazole sodium
- any of the ingredients listed at the end of this leaflet.
- other proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole).

Symptoms of an allergic (hypersensitive) reaction may include:

- rash, itching or hives on the skin
- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body

Do not take PARIET if:

- the packaging is torn or shows signs of tampering.
- the expiry date (month and year) printed on the pack has passed. If you take PARIET after the expiry date it may not work.

PARIET should not be given to children under 18 years of age. Safety and effectiveness of PARIET in children has not been established.

Before you start to take it:

You must tell your doctor if:

- you are pregnant or intend to become pregnant.

- you are breast-feeding or intend to breast-feed. It is not known if PARIET passes into breast milk.
- you have now, or have had in the past, liver problems.

Taking other medicines:

Tell your doctor or pharmacist if you are taking any other medicines, including medicines you can buy without a prescription from a pharmacy, supermarket or health food shop.

Do not take PARIET and tell your doctor or pharmacist if you are taking any of the following:

- atazanavir, a medicine used (with other antiretrovirals) to treat HIV-1 infection.
- clopidogrel, an antiplatelet medicine.

You should not take PARIET while taking these medicines.

Also tell your doctor or pharmacist if you are taking any of the following:

- cyclosporin, a medicine used to treat several conditions including prevention of graft rejection following kidney, liver or heart transplantation; severe, active rheumatoid arthritis; severe skin diseases; kidney disease where other treatments have failed.
- methotrexate, a medicine used to treat some kinds of cancer. It is also used to treat psoriasis (skin disease) and rheumatoid arthritis.
- digoxin, a medicine used to treat heart problems.
- ketoconazole, a medicine used to treat fungal infections.
- mycophenolate mofetil, a medicine used to prevent organ rejection following kidney, liver or heart transplants.
- clarithromycin, a medicine used to treat infections.

These medicines may be affected by PARIET or may affect how well PARIET works. Your doctor or

pharmacist can tell you what to do if you are taking any other medicines.

If you have not told your doctor or pharmacist about any of the above, tell them before you start taking PARIET.

Your doctor will advise you whether or not to take PARIET or if you need to have your dose adjusted.

How to take PARIET

Follow the directions given to you by your doctor and pharmacist carefully. They may differ from the information contained in this leaflet.

How much to take:

Adults

The usual dose is one tablet, to be taken once daily, at the same time each day.

The dose of PARIET tablets is usually 20 mg, but may vary from 10 mg to 40 mg per day depending on what condition you are being treated for and how severe it is.

For treating *Helicobacter pylori* infections in combination with antibiotics (clarithromycin and amoxicillin), the usual dose is one 20mg tablet twice daily, morning and evening, for 7 days.

Children

PARIET should not be given to children under 18 years of age. Safety and effectiveness of PARIET in children has not been established.

How to take it:

- PARIET should be swallowed whole, with a glass of water or other liquid.
- Do NOT crush or chew the tablets. They have a special coating, which protects them from the acid in your stomach. If the coating is broken by chewing, the tablets may not work.

- It does not matter if you take PARIET with food or on an empty stomach.

Ask your doctor or pharmacist for help if you do not understand the instructions provided with this medicine.

If you forget to take it:

If you forget to take your tablet, take it as soon as you remember and then continue to take it as you would normally.

However, if it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you are not sure what to do, check with your doctor or pharmacist.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you have taken too much (overdose):

If you think that you, or anyone else, may have taken too much PARIET, immediately telephone your doctor or the Poisons Information Centre (telephone 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

While you are using PARIET

Things you must do:

- Use PARIET exactly as your doctor has prescribed.
- Always swallow PARIET tablets whole.
- Tell your doctor if you become pregnant while you are taking PARIET

Tell your doctor or pharmacist that you are taking PARIET if you are about to start taking a new medicine.

Things you must not do:

- Do not use PARIET to treat any other complaint unless your doctor says to.
- Do not give this medicine to anyone else, even if they have the same symptoms as you.
- Do not crush or chew the tablets.
- Do not give PARIET to children.

Tell your doctor if you need to have a specific blood test (Chromogranin A) while you are taking PARIET.

It may affect the results of this test.

Side Effects

PARIET is usually well tolerated but tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking PARIET.

PARIET helps most people with peptic ulcers or reflux disease, but it may have unwanted side effects in a few people.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some side effects.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor if you notice any of the following and they worry you:

- headache
- dizziness
- diarrhoea
- nausea
- stomach pain
- wind

- vomiting
- constipation
- runny or blocked nose
- sore throat and discomfort when swallowing
- cough
- pain (including back, chest or joint pain)
- muscle weakness, physical weakness or lack of energy
- rash or itchy rash accompanied by skin eruptions or blisters
- flu-like symptoms
- sleeplessness (insomnia)
- indigestion
- belching
- dry mouth
- leg cramps
- swelling of the arms or legs
- nervousness
- sleepiness (somnolence)
- loss of appetite for food (anorexia)
- weight gain
- sweating

These side effects are usually mild.

Tell your doctor immediately if you notice any of the following:

- painful and/or frequent urination (common symptoms of a urinary tract infection)
- vision or taste disturbance
- depression
- feeling dizzy, faint, lightheaded or weak (hypotension)
- shortness of breath
- signs of frequent infections such as fever, chills, sore throat or mouth ulcers.

These are serious side effects. You may need urgent medical attention. Serious side effects are rare.

Tell your doctor immediately and do not take your next dose of PARIET if you experience:

- signs of allergy such as skin rash, reddening, blisters or itching,

swelling of the face, lips or other parts of the body, shortness of breath or wheezing.

If you experience symptoms such as severe (watery or bloody) diarrhoea, fever, abdominal pain or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation).

Other problems are more likely to arise from the ulcer itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

Under rare circumstances supervised by the doctor, proton pump inhibitors (PPIs) might be used for long periods of time.

Low magnesium can occur in some people who take a proton pump inhibitor. Symptoms of low magnesium can include: seizures, dizziness, spasms, cramps or muscle weakness.

People who take proton pump inhibitor medicines at high doses for a long period of time (1 year or longer) may have an increased risk of fractures of the hip, wrist, or spine.

Proton pump inhibitors may reduce the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor or pharmacist about the possibility of vitamin B-12 deficiency if you have been taking a proton pump inhibitor for a long time (i.e. more than 3 years).

Other side effects not listed above may also occur in some people. Tell your doctor if you notice anything making you feel unwell when you are taking, or soon after you have finished taking PARIET.

Ask your doctor or pharmacist if you do not understand anything in this list.

After using PARIET

Storage

PARIET tablets are packaged in a double-sided aluminium blister strip.

Do not take PARIET tablets out of the blister pack until it is time to take them. If you take them out of the blister they may not keep well.

Keep PARIET tablets in a cool dry place where the temperature is below 25°C. Do not keep PARIET in the refrigerator or freezer.

Do not store PARIET, or any other medicine, in the bathroom or near a sink. Do not leave medicines in the car or on window sills. Heat and dampness can destroy some medicines.

Keep your medicines where children cannot reach them. A locked cupboard at least one-and-a-half metres (1.5 m) above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking PARIET tablets, or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets that are left over.

Product Description

What PARIET tablets look like:

PARIET 10 mg tablets are pink and have "E241" in black ink on one side.

PARIET 20 mg tablets are pale yellow, and have "E243" in red ink on one side.

PARIET 10 mg tablets are supplied in blister packs of 7, 28 and 30 tablets.

PARIET 20 mg tablets are supplied in blister packs of 7, 28 and 30 tablets

Ingredients

Each PARIET tablet contains 10 mg or 20 mg of rabeprazole sodium as the active ingredient.

Each tablet also contains the following other ingredients:

- mannitol, magnesium oxide, hyprolose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide and carnauba wax.
- the 20 mg tablets also contain iron oxide yellow (E172) and are printed with red ink (Edible Ink Red A1).
- the 10 mg tablets contain iron oxide red (E172) and are printed with gray ink (Edible Ink Gray F6).

The tablets do not contain lactose or gluten.

Sponsor

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Rd

Macquarie Park NSW 2113 Australia

Telephone: Toll Free 1800 226 334

Registration Numbers:

PARIET 10mg AUST R 76185

PARIET 20mg AUST R 76186

This leaflet was prepared in August 2018.

PARIET® is a trademark of Eisai Ltd.

Consumer Medicine Information (CMI) summary

The [full CMI](#) on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I using PARIET?

PARIET contains the active ingredient rabeprazole sodium. PARIET is used to treat gastro-oesophageal reflux disease, peptic ulcers, and chronic gastritis in adults.

For more information, see Section [1. Why am I using PARIET?](#) in the full CMI.

2. What should I know before I use PARIET?

Do not use if you have ever had an allergic reaction to rabeprazole sodium or any of the ingredients listed at the end of the CMI.

Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

For more information, see Section [2. What should I know before I use PARIET?](#) in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with PARIET and affect how it works.

A list of these medicines is in Section [3. What if I am taking other medicines?](#) in the full CMI.

4. How do I use PARIET?

- Use PARIET exactly as your doctor has prescribed. The dose of PARIET tablets is usually 20 mg but may vary from 10 mg to 40 mg per day depending on what condition you are being treated for and how severe it is.
- The usual dose is one tablet, to be taken once daily at the same time each day. Always swallow PARIET tablets whole.

More instructions can be found in Section [4. How do I use PARIET?](#) in the full CMI.

5. What should I know while using PARIET?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using rabeprazole sodium. • Use PARIET exactly as your doctor has prescribed. • Tell your doctor if you need to have a specific blood test (Chromogranin A) while you are taking PARIET.
Things you should not do	• Do not give this medicine to anyone else, even if they have the same symptoms as you. • Do not crush or chew the tablets.
Driving or using machines	• Make sure you know how you react to PARIET before you drive a car, operate machinery, or do anything else that could be dangerous if you are dizzy.
Looking after your medicine	• Keep PARIET tablets in a cool dry place where the temperature is below 25°C. Do not keep PARIET in the refrigerator or freezer. • Do not take PARIET tablets out of the blister pack until it is time to take them.

For more information, see Section [5. What should I know while using PARIET?](#) in the full CMI.

6. Are there any side effects?

PARIET is usually well tolerated but tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking PARIET. The common side effects include headache, dizziness, diarrhoea, nausea, abdominal pain, wind, vomiting, constipation, runny or blocked nose, sore throat, cough, non-specific pain, back pain, muscle pain, rash, muscle weakness, physical weakness or lack of energy, flu-like syndrome, infection, insomnia, and chest pain. The serious side effects include allergic reactions; frequent infections; urinary tract infection, vision or taste disturbance, depression, feeling dizzy, faint, lightheaded or weak (hypotension), pain or indigestion, begin to vomit blood or food, pass black (blood-stained) stools, symptoms of bowel inflammation such as severe (watery or bloody) diarrhoea, fever, abdominal pain or tenderness.

For more information, including what to do if you have any side effects, see Section [6. Are there any side effects?](#) in the full CMI.

PARIET® Tablets

Active ingredient(s): *rabeprazole sodium*

Consumer Medicine Information (CMI)

This leaflet provides important information about using PARIET. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using PARIET.**

Where to find information in this leaflet:

1. [Why am I using PARIET?](#)
2. [What should I know before I use PARIET?](#)
3. [What if I am taking other medicines?](#)
4. [How do I use PARIET?](#)
5. [What should I know while using PARIET?](#)
6. [Are there any side effects?](#)
7. [Product details](#)

1. Why am I using PARIET?

PARIET contains the active ingredient rabeprazole sodium. PARIET belongs to a group of medicines called proton pump inhibitors (PPIs). PARIET works by decreasing the amount of acid the stomach makes to give relief from the symptoms and allow healing to take place. Your food will still be digested in the same way.

PARIET is used to treat:

- **Gastro-oesophageal reflux disease:**
PARIET is used to treat gastro-oesophageal reflux disease (GORD), commonly known as 'reflux'. This can be caused by food and acid from the stomach flowing the wrong way (reflux) back up the food pipe, also known as the oesophagus.
Reflux can cause a burning sensation in the chest, rising up to the throat, also known as heartburn. PARIET is also used to help stop gastro-oesophageal reflux disease from coming back or relapsing.
- **Peptic Ulcers:**
PARIET is used to treat peptic ulcers. Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum, which is the tube leading out of the stomach.
These ulcers can be caused by too much acid being made in the stomach.
Most people who have a peptic ulcer also have bacteria called *Helicobacter pylori* in their stomach. Your doctor may also prescribe a course of antibiotics (clarithromycin and amoxycillin) for you. When PARIET is taken with antibiotics, the combination therapy will kill the *Helicobacter pylori* and let your ulcer heal.
- **Chronic Gastritis:**
The presence of the bacteria *Helicobacter pylori* may cause the stomach to become inflamed, resulting in pain, nausea and vomiting; all of which are signs of chronic gastritis.
When PARIET tablets are taken with antibiotics, they

will help kill *Helicobacter pylori* and allow the stomach to heal.

Your doctor may have prescribed PARIET for another reason. Ask your doctor if you have any questions about why PARIET has been prescribed for you.

2. What should I know before I use PARIET?

Warnings

Do not use PARIET if:

- you are allergic to rabeprazole sodium, other PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole), or any of the ingredients listed at the end of this leaflet.
- Always check the ingredients to make sure you can use this medicine.
- the packaging is torn or shows signs of tampering.

Check with your doctor if you:

- have now, or have had in the past, liver problems
- take any medicines for any other condition

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section [6. Are there any side effects?](#)

Pregnancy and breastfeeding

Check with your doctor if you are pregnant or intend to become pregnant.

Talk to your doctor if you are breastfeeding or intend to breastfeed. It is not known if PARIET passes into breast milk.

Children and adolescents

PARIET should not be given to children under 18 years of age. Safety and effectiveness of PARIET in children has not been established.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with PARIET and affect how it works.

Do not take PARIET and tell your doctor or pharmacist if you are taking any of the following:

- atazanavir, a medicine used (with other antiretrovirals) to treat HIV-1 infection.
- clopidogrel, an antiplatelet medicine.

You should not take PARIET while taking these medicines.

Also tell your doctor or pharmacist if you are taking any of the following:

- cyclosporin, a medicine used to treat several conditions including prevention of graft rejection following kidney, liver or heart transplantation; severe, active rheumatoid arthritis; severe skin diseases; kidney disease where other treatments have failed.
- methotrexate, a medicine used to treat some kinds of cancer. It is also used to treat psoriasis (skin disease) and rheumatoid arthritis.
- digoxin, a medicine used to treat heart problems.
- ketoconazole, a medicine used to treat fungal infections.
- mycophenolate mofetil, a medicine used to prevent organ rejection following kidney, liver or heart transplants.
- clarithromycin, a medicine used to treat infections.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect PARIET.

4. How do I use PARIET?

How much to take

- The usual dose is one tablet to be taken once daily.
- The dose of PARIET tablets is usually 20 mg but may vary from 10 mg to 40 mg per day depending on what condition you are being treated for and how severe it is.
- For treating *Helicobacter pylori* infections in combination with antibiotics (clarithromycin and amoxycillin), the usual dose is one 20mg tablet twice daily, morning and evening, for 7 days.
- Follow the instructions provided and use PARIET until your doctor tells you to stop.

When to take PARIET

- PARIET should be taken at the same time each day.

How to take PARIET

- PARIET should be swallowed whole, with a glass of water or other liquid.
- Do NOT crush or chew the tablets. They have a special coating, which protects them from the acid in your stomach. If the coating is broken by chewing, the tablets may not work.
- It does not matter if you take PARIET with food or on an empty stomach

If you forget to use PARIET

If you miss your dose at the usual time, take it as soon as you remember and then continue to take it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you use too much PARIET

If you think that you have used too much PARIET, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (by calling 13 11 26), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using PARIET?

Things you should do

- Use PARIET exactly as your doctor has prescribed.
- **Tell your doctor if you need to have a specific blood test (Chromogranin A) while you are taking PARIET.** It may affect the results of this test.

Call your doctor straight away if you:

- become pregnant while you are taking PARIET

Remind any doctor, dentist or pharmacist you visit that you are using PARIET.

Things you should not do

- Do not use PARIET to treat any other complaints unless your doctor says to.
- Do not give this medicine to anyone else, even if they have the same symptoms as you.
- Do not crush or chew the tablets.
- Do not give PARIET to children.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how PARIET affects you.

PARIET may cause dizziness in some people.

Looking after your medicine

- Do not take PARIET tablets out of the blister pack until it is time to take them. PARIET tablets are packaged in a double-sided aluminium blister strip. If you take them out of the blister they may not keep well.
- Keep PARIET tablets in a cool dry place where the temperature is below 25°C. Do not keep PARIET in the refrigerator or freezer.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on window sills.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres (1.5 m) above the ground is a good place to store medicines.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
Brain or nervous system related: - headache - sleeplessness (insomnia) - sleepiness (somnolence) - nervousness Stomach or bowel related: - nausea - vomiting - stomach pain - belching or indigestion - wind - diarrhoea - constipation Skin related: - rash or itchy rash accompanied by skin eruptions or blisters Muscle or joint related: - pain (including back or joint pain) - leg cramps - muscle weakness, physical weakness or lack of energy Breathing related: - cough - flu-like symptoms - runny or blocked nose - sore throat and discomfort when swallowing Other: - dry mouth - swelling of the arms or legs - loss of appetite for food (anorexia) - weight gain - sweating	Speak to your doctor if you have any of these less serious side effects and they worry you.

Less serious side effects	What to do
Long-term use related (when PPIs might be used for long periods of time under rare circumstances supervised by the doctor): - Low magnesium can occur in some people who take a PPI. Symptoms of low magnesium can include seizures, dizziness, spasms, cramps or muscle weakness: - Low magnesium can lead to low calcium and/or low potassium levels in blood. - PPIs may reduce the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor or pharmacist about the possibility of vitamin B-12 deficiency if you have been taking a PPI for a long time (i.e. more than 3 years). - People who take PPI medicines at high doses for a long period of time (1 year or longer) may have an increased risk of fractures of the hip, wrist, or spine. - Withdrawal of long-term PPI therapy may lead to worsening of acid-related symptoms.	

Serious side effects

Serious side effects	What to do
Allergic reactions: - skin rash, reddening, blisters or itching on the skin - shortness of breath or wheezing - swelling of the face, lips or other parts of the body Infection related: - signs of frequent infections such as fever, chills, sore throat or mouth ulcers - common symptoms of a urinary tract infection such as painful and/or frequent urination Brain or nervous system related: - vision or taste disturbance - depression - feeling dizzy, faint, lightheaded or weak (hypotension) Heart related: - chest pain Stomach or bowel related:	Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.

Serious side effects	What to do
- pain or indigestion that may be related to the ulcer itself - begin to vomit blood or food - pass black (blood-stained) stools - symptoms of <i>Clostridium difficile</i> colitis (bowel inflammation) such as severe (watery or bloody) diarrhoea, fever, abdominal pain or tenderness	

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people and are more likely to arise from the ulcer itself rather than the treatment.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What PARIET contains

Active ingredient (main ingredient)	rabeprazole sodium
Other ingredients (inactive ingredients)	mannitol, magnesium oxide, hypromellose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, purified talc, titanium dioxide, carnauba wax The 20 mg tablets also contain iron oxide yellow and are printed with red ink (Edible Ink Red A1). The 10 mg tablets contain iron oxide red and are printed with gray ink (Edible Ink Gray F6).

Do not take this medicine if you are allergic to any of these ingredients.

The tablets do not contain lactose or gluten.

What PARIET looks like

PARIET 10 mg tablets are pink and have "E241" in black ink on one side (Aust R 76185).

PARIET 10 mg tablets are available in blister packs of 7, 28 and 30 tablets.

PARIET 20 mg tablets are pale yellow and have "E243" in red ink on one side (Aust R 76186).

PARIET 20 mg tablets are available in blister packs of 7, 28 and 30 tablets.

Not all pack sizes may be marketed.

Who distributes PARIET

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Rd

Macquarie Park NSW 2113 Australia

Telephone: Toll Free 1800 226 334

This leaflet was prepared in August 2025.

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