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 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 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 ^{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.

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 (≥ 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 (≥ 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 (≥ 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 ($p\leq0.003$) 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 $\pm$ 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 $\leq$ 5 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, $AUC_{0-\infty}$ 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 **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, hyprolose, 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

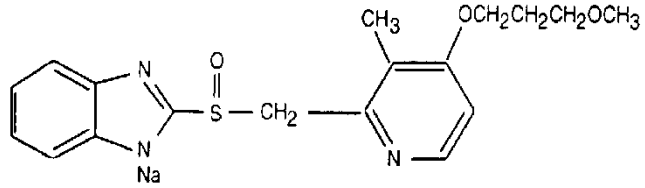
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name for rabeprazole sodium is (±) 2-[{4-(3-methoxypropoxy)-3-methylpyridin-2-yl}-methylsulphinyl]-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,

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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