

DATA SHEET

NAME OF MEDICINE

PARIET™ rabeprazole sodium 10 mg and 20 mg tablets

PRESENTATION

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, acetylated monoglycerides, purified talc, titanium dioxide and carnauba wax. The 10 mg tablet also contains iron oxide red CI 77491 and Opacode S-1-17740 and the 20 mg tablet contains iron oxide yellow CI 77499 and Opacode S-1-16507.

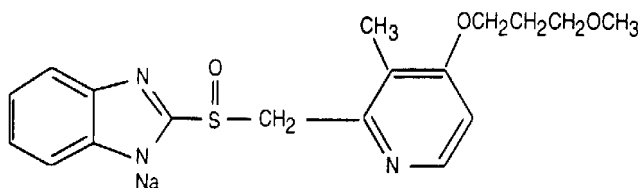
PARIET 10mg and 20mg tablets are not currently marketed in New Zealand.

USES

Actions

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:



CAS-117976-89-3

C₁₈H₂₀N₃NaO₃S

MW: 381.43

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. The substituted benzimidazoles do not exhibit anticholinergic or histamine antagonistic properties. 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* therapy is appropriate in most patients with duodenal and gastric ulcers 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.

Human gastric biopsy specimens from the antrum and the fundus from over 500 patients receiving rabeprazole sodium or comparator treatment for up to 8 weeks have not detected changes in ECL cell histology, degree of gastritis, incidence of atrophic gastritis, intestinal metaplasia or distribution of *H. pylori* infection.

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. The absorption of rabeprazole sodium is not affected by food or the time of administration.

Distribution: Rabeprazole sodium is approximately 97% bound to human plasma proteins.

Metabolism: Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolism system (see **Interactions with Other Drugs**). Five metabolites were observed in human plasma. 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. These metabolites are not observed to have antisecretory activity.

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. 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/1.73m²), the pharmacokinetics of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic Disease: In patients with mild to moderate chronic hepatic disease, the AUC doubled reflecting a decreased first-pass effect; the t_{1/2} (plasma half-life) increased 2-3 fold, and the C_{max} increased by 50% when compared to healthy subjects matched according to age and sex. However, there was no evidence of significant drug related safety problems.

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% and t_{1/2} increased by approximately 30% as compared to young healthy volunteers. However, there was no evidence of rabeprazole sodium accumulation.

Indications

PARIET is indicated for:

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

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.

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. Although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.

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.

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.

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 + amoxicillin 1 g twice daily for seven days.

The US National Institute of Health has recommended that regimens to *eradicate H. pylori* in patients with peptic ulcer disease should contain both anti-secretory agents and anti-microbial agents (to which *H. pylori* has been demonstrated to be sensitive in vivo).

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 or hepatic impairment (see **PRECAUTIONS** for treatment of patients with severe hepatic impairment).

CONTRAINDICATIONS

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

WARNING AND PRECAUTIONS

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

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**).

Carcinogenicity, Mutagenicity and Impairment of Fertility

Pre-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure to make concerns for human safety negligible in respect of animal data.

Studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but *in vivo* micronucleus and *in vivo* and *in vitro* DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

Investigation of the reproductive performance of rats and the reproductive development of the progeny in a two generation perinatal/postnatal study using daily intravenous doses of up to 30 mg/kg/day (about 15 times the human dose based on mg/m²) was conducted. In this study, rabeprazole sodium produced no adverse effects on fertility or general reproduction.

Use in Pregnancy

Category B1.

Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Studies in pregnant women have not been performed. PARIET should therefore only be used during pregnancy if the potential benefit exceeds the potential risk to the foetus.

Use in Lactation

It is not known if rabeprazole sodium is excreted in human breast milk. Studies in lactating women have not been performed. Rabeprazole sodium is however excreted in rat mammary secretions. PARIET should therefore only be used by a woman who is breast-feeding if the potential benefit exceeds the potential risk to the infant.

ADVERSE EFFECTS

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, dry mouth.
<i>Gastrointestinal:</i>	diarrhoea, nausea, abdominal pain, flatulence, vomiting, constipation, dyspepsia, eructation.
<i>Respiratory:</i>	rhinitis, pharyngitis, cough, sinusitis, bronchitis.
<i>Musculoskeletal:</i>	asthenia, non-specific pain, back pain, myalgia, arthralgia, leg cramps.
<i>Skin:</i>	rash.
<i>Urinary:</i>	urinary tract infection.
<i>Other:</i>	flu-like syndrome, infection, insomnia, fever, chest pain, nervousness, somnolence, chills.

Rare ($<0.1\%$)

<i>Nervous System:</i>	depression.
<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.

Post-Marketing Experience

Erythema and rarely bullous reactions have been reported in patients treated with PARIET. These usually resolved after discontinuation of therapy. Thrombocytopenia, neutropenia and leukopenia have been reported rarely. There have also been reports of increased hepatic enzymes.

INTERACTIONS

Effect of rabeprazole sodium on other drugs - demonstrated interactions

Cyclosporin: Studies performed *in vitro* using human liver microsomes indicated that the degree of inhibition of cyclosporin by rabeprazole sodium and omeprazole is similar at equivalent concentrations.

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.

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

Effect of rabeprazole sodium on other drugs - theoretical interactions

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, theophylline, phenytoin and diazepam.

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

OVERDOSAGE

There is no experience to date with deliberate overdose. Dosages of up to 80 mg/day have been well tolerated. 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.

PHARMACEUTICAL PRECAUTIONS

Storage

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

PARIET tablets may be presented in either a clear blister in an aluminium pouch or in an aluminium/aluminium blister. The clear blister strips should be stored in the original aluminium pouch with the desiccant after opening and any remaining tablets should be discarded three months after the pouch is opened.

MEDICINAL CLASSIFICATION

PRESCRIPTION MEDICINE

PACKAGE QUANTITIES

PARIET 10 mg are pink, biconvex tablets, marked “ε 241”

PARIET 20 mg are light yellow, biconvex tablets, marked “ε 243”

PARIET tablets are available in blister packs of, 14, 28, 56, 15, 30, 60 and 2 as a physician's pack.

FURTHER INFORMATION

Clinical trials

Treatment of Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): In the placebo-controlled study, 103 patients were treated for up to eight weeks with a fixed dose of placebo or PARIET 20 mg once daily. 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 provided 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.

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 ($p < 0.001$).

Patients treated with PARIET 20 mg od for six weeks also required significantly fewer daily antacid doses than did patients treated with placebo ($p = 0.039$).

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 therapy for *H. pylori* eradication in patients with peptic ulcer disease, the combination PARIET 20 mg twice daily with clarithromycin 500 mg twice daily and amoxicillin 1 g 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%.

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DATE OF PREPARATION

11 February 2002