Professional Information (PI)

SCHEDULING STATUS
Schedule 4

1. NAME OF THE MEDICINE

PARIET® 10 mg enteric-coated delayed release tablets

PARIET® 20 mg enteric-coated delayed release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PARIET 10 mg: Each enteric-coated delayed release tablet contains 10 mg of rabeprazole sodium, equivalent to 9,42 mg rabeprazole (racemate).

PARIET 20 mg: Each enteric-coated delayed release tablet contains 20 mg of rabeprazole sodium, equivalent to 18,85 mg rabeprazole (racemate).

Contains sugar (mannitol).

PARIET 10 mg: Each tablet contains 26 mg mannitol.

PARIET 20 mg: Each tablet contains 40 mg mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric-coated delayed release tablets.

10 mg: Pink, film-coated biconvex tablets, with or without “E241” printed in black on one side.

20 mg: Light yellow, film-coated biconvex tablets, with or without “E243” printed in red on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PARIET tablets are indicated for the treatment of:

- Active duodenal ulcer.
- Active benign gastric ulcer.
- Symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD).
- Maintenance treatment of healed erosive or ulcerative GORD. Efficacy has not been demonstrated for periods exceeding 12 months.
- Symptomatic treatment of gastro-oesophageal reflux disease (GORD).
- Zollinger-Ellison Syndrome and other pathological hypersecretory conditions.
- *H.Pylori*-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics.

4.2 Posology and method of administration

Posology

Adults and Elderly:

Active Duodenal Ulcer and Active Benign Gastric Ulcer: 20 mg to be taken once daily in the morning.

Most patients with active duodenal ulcer heal within four weeks. However, 2 % of patients may require an additional four weeks of therapy to achieve healing.

Some patients with active duodenal ulcer may respond to one 10 mg tablet to be taken once daily in the morning.

Most patients with active benign gastric ulcer heal within six weeks. However, 9 % of patients may require an additional six weeks of therapy to achieve healing.

Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): 20 mg to be taken once daily for four to eight weeks.

Gastro-Oesophageal Reflux Long – term Management (GORD Maintenance): For long-term management up to 12 months, a maintenance dose of PARIET 10 mg or 20 mg once daily can be used. Some patients may respond to a maintenance dose of 10 mg/day.

Symptomatic treatment of gastro-oesophageal reflux disease (symptomatic GORD): 10 mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved; subsequent symptom control can be achieved using an on-demand regimen taking 10 mg once daily when needed.

Zollinger-Ellison Syndrome and other pathological hypersecretory conditions:
The recommended adult starting dose is 60 mg once a day. The dose may be titrated upwards to 120 mg/day based on individual patient needs. Single daily doses up to 100 mg/day may be given. 120 mg dose may require divided doses, 60 mg twice daily. Treatment should continue for as long as clinically indicated.

Eradication of H.Pylori: PARIET is indicated for *H.Pylori*-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics.

Special populations

Paediatrics:

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

Renal impairment:

No dosage adjustment is necessary for patients with renal impairment.

Hepatic impairment

No dosage adjustment is needed for patients with hepatic impairment. Caution is however advised when PARIET is first initiated in patients with severe hepatic dysfunction, refer section 4.4 “Special warnings and precautions for use- Patients with severe hepatic dysfunction”).

Method of administration

PARIET tablets should be taken in the morning, before eating; and 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.

Patients should be cautioned that the PARIET tablets should not be chewed or crushed, but should be swallowed whole.

4.3 Contraindications

PARIET is contraindicated in:

- Patients with known hypersensitivity to rabeprazole sodium, substituted benzimidazoles or to any of the excipients listed in section 6.1.
- Pregnancy and lactation. (See section 4.6, “Pregnancy and Breastfeeding”).
- Co-administration with atazanavir and nelfinavir.
- Patients who previously experienced acute tubulointerstitial nephritis (TIN) while on treatment with a PPI.

4.4 Special warnings and precautions for use

Pre-existing malignancy

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

Patients with severe hepatic dysfunction

Although no evidence of significant medicine related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls, the prescriber is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported in patients treated with PARIET for at least three months, and in most cases after a year of therapy. Serious adverse events include tetany, dysrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of PARIET.

For patients expected to be on prolonged treatment or who take PARIET with medications such as digoxin or medicines that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PARIET treatment and periodically thereafter. (See section 4.8, “Undesirable Effects”).

Fractures

Observational studies suggest that PARIET 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 PARIET therapy (a year or longer) (See section 4.8 “Undesirable Effects”).

Concomitant use of PARIET with methotrexate

Literature suggests that concomitant use of PARIET 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-related toxicities. In high-dose methotrexate administration, a temporary withdrawal of PARIET may be considered in some patients (See section 4.5 “Interactions”).

Gastrointestinal infections

Treatment with PARIET may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile, Campylobacter* and *Salmonella.*

Concomitant use of PARIET with atazanavir

Co-administration of atazanavir with PARIET is contraindicated. (See section 4.5, “Interactions”).

Influence on vitamin B 12 absorption

PARIET may reduce the absorption of vitamin B 12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B 12 absorption on long-term therapy or if respective clinical symptoms are observed.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of Proton Pump Inhibitors (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 healthcare professional should consider stopping PARIET. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Blood dyscrasias

There have been post marketing reports of blood dyscrasias (thrombocytopaenia and neutropaenia). In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of PARIET.

Fundic gland polyps

Long-term use of PARIET is associated with an increased risk of fundic gland polyps (see section 4.8, "Undesirable effects – Postmarketing data). Most fundic 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 the shortest duration of Proton Pump Inhibitors (PPI) therapy appropriate to the condition being treated.

Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking Proton Pump Inhibitors (PPIs) and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash, or arthralgia). Discontinue PARIET and evaluate patients with suspected acute TIN.

Mannitol intolerance

Patients with the rare hereditary condition of mannitol intolerance should not take PARIET.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 system

Rabeprazole sodium is metabolised through the cytochrome P450 (CYP450) hepatic metabolising system. Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with other medicines metabolised by the CYP450 system, such as warfarin, phenytoin, theophylline or diazepam.

Interactions due to inhibition of gastric acid secretion

Rabeprazole sodium produces a profound and long-lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur; therefore, the potential for such interaction was investigated. Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal levels and a 22 % increase in trough digoxin levels in normal subjects. Therefore, individual patients may need to be monitored to determine if a dosage adjustment is necessary when such medicines are taken concomitantly with PARIET.

Antacids

In clinical trials, antacids were used concomitantly with the administration of PARIET and, in a specific interaction study, no interaction with liquid antacids was observed.

Food

There was no clinically relevant interaction with food.

Ciclosporin

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). The studies suggest a low interaction potential; however, the effect on ciclosporin metabolism is similar to that observed for other proton pump inhibitors.

Atazanavir

Co-administration of atazanavir 300 mg/ritonavir 100 mg or atazanavir 400 mg with other proton pump inhibitors (PPIs) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with rabeprazole. Therefore PPIs, including PARIET, should not be co-administered with atazanavir (See section 4.3, "Contraindications" and section 4.4, "Special warnings and precautions for use").

Methotrexate

Concomitant administration of PARIET 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 interaction studies of methotrexate with PARIET have been conducted.

Digoxin

In healthy subjects (n=16), co-administration of PARIET 20 mg at steady state with 2,5 mg once daily doses of digoxin at steady state resulted in approximately 29 % and 19 % increase in mean C_{max} and AUC $_{(0-24)}$ of digoxin. Monitor digoxin concentrations for potential for increased exposure to digoxin. Dose adjustment of digoxin may be needed to maintain therapeutic medicine concentrations.

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 tumours. 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.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

Low foeto-placental transfer occurs in rats. PARIET is contraindicated during pregnancy (see section 4.3, “Contraindications”).

Breastfeeding

Excretion of rabeprazole sodium in human breast milk has not been studied. Rabeprazole sodium is excreted in rat mammary secretions. Therefore mothers on treatment with PARIET should not breastfeed their babies (See section 4.3, “Contraindications”).

4.7 Effects on ability to drive and use machines

Based on pharmacodynamic properties and adverse events profile, it is unlikely that PARIET would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8 Undesirable effects

The most common adverse events, during controlled clinical trials with PARIET, were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth.

The following adverse events have been reported from clinical trial experience by system organ class and frequency.

Clinical trials

System organ class	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10 000, <1/1000)	Very rare (<1/10 000)	Not known
Infections and infestations	Infection, including *Salmonella*				
Blood and the lymphatic system disorders			Leucocytosis		
Metabolism and nutrition disorders			Anorexia		Hypo-natraemia
Psychiatric disorders	Insomnia	Nervousness	Depression		Confusion
Nervous system disorders	Headache Dizziness	Somnolence			
Eye disorders			Visual disturbances		
Vascular disorders					Peripheral oedema
Respiratory, thoracic and mediastinal disorders	Cough Pharyngitis Rhinitis	Bronchitis Sinusitis			

Gastrointestinal disorders	Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbances Gastric glandular cysts		
Skin and subcutaneous tissue disorders		Rash	Pruritus Sweating		
Musculoskeletal, connective tissue and bone disorders	Non-specific pain/back pain	Myalgia Leg cramps Arthralgia Fracture of the hip, wrist or spine			
Renal and urinary disorders		Urinary tract infection			

General disorders and administration site conditions	Asthenia Flu-like syndrome	Chest pain Chills Fever			
Investigations			Weight gain		

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience.

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

Hypomagnesemia, thrombocytopenia, neutropenia and leucopenia have been reported. There have been reports of increased hepatic enzymes and reports of hepatitis or jaundice.
Reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been reports of acute tubulointerstitial nephritis*, gynaecomastia, erythema multiforme, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome. There have been post-marketing reports of bone fractures, subacute cutaneous lupus erythematosus (SCLE) and fundic gland polyps (see section 4.4, Special warnings and precautions for use).

*The renal effect may progress to acute kidney injury and/or chronic renal failure. The symptoms of acute tubulointerstitial nephritis may persist even when treatment with PPI, including PARIET, is terminated.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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, similar to the known adverse event profile, and usually reversible without further medical intervention.

No specific antidote is known. Rabeprazole sodium is extensively protein bound and is, therefore, not readily dialysable. Treatment should be supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism, Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), PPIs, ATC code: A02B C04.

Mechanism of action

Rabeprazole sodium is a gastric proton-pump inhibitor, 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.

Anti-secretory activity:

After oral administration of a 20 mg dose of rabeprazole sodium 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 are 69 % and 82 % respectively and the duration of inhibition lasts up to 48 hours. This 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 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 medicine 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 24 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.

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with amoxicillin. Rabeprazole sodium does not adversely influence plasma concentrations of amoxicillin or clarithromycin when co-administered for the purpose of eradicating upper gastrointestinal *H.pylori* infection.

5.2 Pharmacokinetic properties

Absorption

Rabeprazole sodium is acid-labile, and is therefore administered orally as an enteric-coated (gastro-resistant) tablet formulation. Absorption of rabeprazole sodium therefore begins only after the tablet leaves the stomach. 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 % due in large part 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. In patients with chronic hepatic disease, the AUC doubled compared to healthy volunteers, reflecting a decreased first-pass effect, and the plasma half-life increased 2-3 fold.

Distribution

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

Metabolism

The main plasma metabolites are thioether (M1) and carboxylic acid (M6). Minor metabolites observed at lower levels include sulphone (M2), desmethyl-thioether (M4)

and mercapturic acid conjugate (M5). Only the desmethyl metabolite (M3) has a small amount of antisecretory activity, but it is not present in plasma.

Excretion

Excretion is mainly urinary (90 %), with no unchanged active excreted in the urine. The rest of the metabolites are excreted via the faeces. Total recovery was 99,8 % implying a low biliary excretion of the metabolites of rabeprazole sodium.

Special populations

Gender

Adjusted for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single 20 mg dose of rabeprazole.

Elderly

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

Renal impairment

In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1,73 m^2), the disposition of rabeprazole sodium was very similar to that in healthy volunteers.

Hepatic impairment

Following a single 20 mg dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3 fold increase in half-life of rabeprazole compared to the healthy volunteers. However, following a 20 mg dose daily for 7 days the AUC had increased to only 1.5-fold and the C_{max} to only 1.2-fold. The half-life of rabeprazole in patients with hepatic impairment was 12,3 hours compared to 2,1 hours in healthy volunteers. The pharmacodynamic response (gastric pH control) in the two groups was clinically comparable.

CYP2C19 Polymorphism

Following a 20 mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and $t_{½}$ which were approximately 1,9 and 1,6 times the corresponding parameters in extensive metabolisers whilst C_{max} had increased by only 40 %.

5.3 Preclinical safety data

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

Carcinogenicity and mutagenicity

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Mannitol, magnesium oxide, low-substitutued hyprolose, hyprolose, magnesium stearate.

Undercoating:

Ethylcellulose, magnesium oxide.

Enteric coating:

Hypromellose phthalate, diacetylated monoglycerides, talc, titanium dioxide (E171), red iron oxide (E172) – 10 mg only, yellow iron oxide (E172)-20 mg only, carnauba wax.

Printing ink - PARIET 10 mg:

White shellac, black iron oxide (E172), dehydrated ethyl alcohol, 1-butanol.

Printing ink - PARIET 20 mg:

White shellac, red iron oxide (E172), carnauba wax, glycerine fatty acid ester, dehydrated ethyl alcohol, 1-butanol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture. Do not store in the refrigerator.

Keep out of reach of children.

6.5 Nature and contents of container

Primary packaging:

Unit dose blister strips (aluminium/aluminium blister) of 14 tablets.

6.6 Special precautions for disposal and other handling

No special instructions.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION



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8. REGISTRATION NUMBER(S)

PARIET 10 mg: 33/11.4.3/0206

PARIET 20 mg: 32/11.4.3/0614

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 24 February 2000

10. DATE OF REVISION OF THE TEXT

11 February 2025