NAME OF THE MEDICINAL PRODUCT

Tradename

PARIET®

International Non-Proprietary Name

rabeprazole sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains:
9.42 mg rabeprazole as 10 mg rabeprazole sodium or
18.85 mg rabeprazole as 20 mg rabeprazole sodium.

PHARMACEUTICAL FORM

Gastro-resistant tablets.

CLINICAL PARTICULARS

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);
- Gastro-Oesophageal Reflux Disease Long-term Management (GORD Maintenance);
- symptomatic gastro-oesophageal reflux disease (symptomatic GORD).

In combination with appropriate antibacterial therapeutic regimens for:

- the eradication of Helicobacter pylori in patients with peptic ulcer disease or chronic gastritis;
- the healing and the prevention of relapse of peptic ulcers in patients with *H. pylori* associated ulcers.

Posology and Method of Administration

Adults/Elderly

Active Duodenal Ulcer and Active Benign Gastric Ulcer:

The recommended oral dose for both active duodenal ulcer and active benign gastric ulcer is 20 mg to be taken once daily in the morning.

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 duodenal ulcer heal within two to four weeks. A few refractory patients may require an additional four weeks of therapy to achieve healing. Most patients with active benign gastric ulcer heal within six weeks. A few refractory patients may require an additional six weeks of therapy to achieve healing.

Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD):

The recommended oral dose for this condition is 20 mg to be taken once daily for four to eight weeks.

Gastro-Oesophageal Reflux Disease Long-term Management (GORD Maintenance):

For long-term management, a maintenance dose of PARIET 10 mg or 20 mg once daily can be used depending upon patient response.

Symptomatic gastro-oesophageal reflux disease (symptomatic GORD):

10 mg or 20 mg once daily in patients without oesophagitis. If symptom control has not been achieved during 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.

Eradication of H. pylori:

Patients with gastro-duodenal ulcers or chronic gastritis due to *H. pylori* infection should be treated with eradication therapy with appropriate combinations of antibiotics. One of the following combinations given for 7 days is recommended.

- PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and amoxycillin 1 g twice daily or
- PARIET 20 mg twice daily + clarithromycin 500 mg twice daily and metronidazole 400 mg twice daily.

The best eradication results, which exceed 90%, are obtained when rabeprazole is used in combination with clarithromycin and amoxycillin. For further information on the other components of the *H. pylori* eradication therapy see the individual product data sheet.

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

For indications requiring once daily treatment, 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.

For *H. pylori* eradication, PARIET — in combination regimens with two appropriate antibiotics — should be taken twice daily.

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

Renal and hepatic impairment:

No dosage adjustment is necessary for patients with renal or hepatic impairment. See section “Special Warnings and Precautions for Use” in the treatment of patients with severe hepatic impairment.

Children

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

Contraindications

PARIET is contraindicated in patients with known hypersensitivity to rabeprazole sodium, substituted benzimidazoles or to any excipient used in the formulation. PARIET is contra-indicated in pregnancy and during breast-feeding.

Special Warnings and Special 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

No evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls. However because there are no clinical data on the use of PARIET in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with PARIET is first initiated in such patients.

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically (see Undesirable Effects).

Interactions with Other Medicinal Products and Other Forms of Interaction

Cytochrome P450 System

Rabeprazole sodium, as is the case with other members of the proton pump inhibitor (PPI) class of compounds, is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolising system. Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with the drugs studied including warfarin, phenytoin, theophylline or diazepam metabolised by the CYP450 system.

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 results in a 33% decrease in ketoconazole 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 drugs are taken concomitantly with PARIET.

Antacids

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

Food

There was no clinically relevant interaction with food.

Cyclosporin

In vitro studies with human liver microsomes indicated that rapebrazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In these studies, at expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and although *in vitro* studies may not always be predictive of in vivo status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

Atazanavir

Co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although co-administration with rabeprazole was not studied, similar results are expected with other proton pump inhibitors. Therefore PPIs, including rabeprazole, should not be coadministered with atazanavir.

Pregnancy and Lactation

Pregnancy

There are no data on the safety of rabeprazole in human pregnancy.

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. PARIET is contraindicated during pregnancy.

Lactation

It is not known whether rabeprazole sodium is excreted in human breast milk. No studies in lactating women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore PARIET should not be used during breast-feeding.

Effects on Ability to Drive and Use Machines

Based on the pharmacodynamic properties and the 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.

Undesirable Effects

Clinical Trials

PARIET was generally well tolerated during clinical trials. The observed undesirable effects have generally been mild/moderate and transient in nature.

In clinical trials, the most common adverse events (incidence ≥5%) were headache, diarrhoea and nausea.

Other adverse events (incidence <5% and ≥2%) were rhinitis, abdominal pain, asthenia, flatulence, pharyngitis, vomiting, non-specific pain/back pain, dizziness, flu like syndrome, infection, cough, constipation and insomnia. Further less frequent adverse events (incidence ≤1%) were rash, myalgia, chest pain, dry mouth, dyspepsia, nervousness, somnolence, bronchitis, sinusitis, chills, eructation, leg cramps, urinary tract infection, arthralgia, and fever.

In isolated cases, anorexia, gastritis, weight gain, depression, pruritus, vision or taste disturbances, stomatitis, sweating, leucocytosis have been observed.

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

Post-marketing 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 rarely.

There have been reports of increased hepatic enzymes and rarely reports of hepatitis or jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.

There have been very rare reports of interstitial nephritis, gynaecomastia, erythema multiforme, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome.

Overdose

Animal Study Data

LD_{50} of rabeprazole sodium after single oral administration is >1000 mg/kg in mice, >1300 mg/kg in rats. The lethal dose of rabeprazole sodium after single oral administration is >2000 mg/kg in dogs (approximately 2500 to 5000 times the recommended human dose, ie, 20 mg/day), and is >200 mg/kg in mice and >150 mg/kg in rats, by single intravenous injection. Peak plasma levels in animals are 8 to

37 times the human peak concentration (Cmax=427 ng/mL) after the first oral dose of 100 mg/kg in mice, 300 mg/kg in rats and 25 mg/kg in dogs.

Symptoms

Experience with deliberate or accidental overdose is limited. There has been no experience with large overdoses with rabeprazole. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable.

Treatment

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 utilised.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Alimentary tract and metabolism, Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors.

ATC code: A02B C04

Mechanism of Action

Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme (the acid or proton pump). The 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. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

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. 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 acid peptic disease including duodenal ulcer (DU) and gastric ulcer (GU). *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.

Rabeprazole has been shown to have a bactericidal effect on *H. pylori in vitro*. Eradication of *H. pylori* with PARIET (rabeprazole) and antimicrobials is associated with high rates of healing of mucosal lesions. Clinical experience from controlled randomised clinical trials indicate that rabeprazole 20 mg twice daily in combination with two antibiotics e.g. clarithromycin and amoxycillin or clarithromycin and metronidazole (given at approved dose levels) for 1 week achieve >80% *H. pylori*

eradication rate in patients with gastro-duodenal ulcers. As expected, there was a trend towards significantly lower eradication rates in patients with baseline metronidazole resistant *H. pylori* isolates and a trend towards the development of secondary resistance. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken in account in the choice of an appropriate combination regimen for *H. pylori* eradication therapy. Further more, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antibacterial agent should be taken into account in the considerations for a new re-treatment regimen.

Serum Gastrin Effects

In clinical studies patients were treated once daily with 10 or 20 mg rabeprazole sodium, for up to 43 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion and remained stable while treatment was continued. 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 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. In over 250 patients followed for 36 months of continuous therapy, no significant change in findings present at baseline was observed.

Other Effects

Systemic effects of rabeprazole sodium in the CNS, cardiovascular and respiratory systems have not been found to date. Rabeprazole sodium, given in oral doses of 20 mg for 2 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, oestrogen, testosterone, prolactin, cholecystokinin, secretin, glucagon, follicle stimulating hormone (FSH), luteinising hormone (LH), renin, aldosterone or somatotrophic hormone.

Pharmacokinetic Properties

Absorption

PARIET is an enteric-coated (gastro-resistant) tablet formulation of rabeprazole sodium. This presentation is necessary because rabeprazole is acid-labile. Absorption of rabeprazole therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole 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. Neither food nor the time of day of administration of the treatment affect the absorption of rabeprazole sodium.

Distribution

Rabeprazole is approximately 97% bound to human plasma proteins.

Metabolism and excretion

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 it is not present in plasma.
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. The remainder of the dose was recovered in faeces.
Gender
Adjusted for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single 20 mg dose of rabeprazole.
Renal dysfunction
In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤5ml/min/1.73m^2), the disposition of rabeprazole was very similar to that in healthy volunteers. The AUC and the C_{max} in these patients was about 35% lower than the corresponding parameters in healthy volunteers. The mean half-life of rabeprazole was 0.82 hours in healthy volunteers, 0.95 hours in patients during haemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients with renal disease requiring maintenance haemodialysis was approximately twice that in healthy volunteers.
Hepatic dysfunction
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.
Elderly
Elimination of rabeprazole 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% and $t_{½}$ increased by approximately 30% as compared to young healthy volunteers. However there was no evidence of rabeprazole accumulation.
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%.

Preclinical Safety Data

Pre-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Mannitol, magnesium oxide, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, talc, titanium dioxide, yellow iron oxide (20 mg only), red iron oxide (10 mg only), carnauba wax and ink.

Incompatibilities

Not applicable.

Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage

Do not store above 25°C. Do not refrigerate.

After opening, store in the original package (aluminium pouch) and use within 3 months.

Keep out of reach of children.

Nature and Contents of Container

Primary packaging:

Unit dose blister strips (PVC/PVdC/PE-5ply laminate/aluminium foil strip) of 7 or 14 tablets.

Secondary packaging:

Aluminium pouch containing multiples of 7 or 14 tablet unit dose blister strips and a silica gel desiccant pouch.

Alternative packaging Format:

Primary packaging:

Unit dose blister strips (aluminium/aluminium) of 7 or 14 tablets.

Instructions for Use and Handling

No special instructions.

MANUFACTURED BY

See outer carton.

DATE OF REVISION OF THE TEXT

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