SCHEDULING STATUS

Schedule 4

PROPRIETARY NAME (and dosage form)

PARIET® 10 mg tablets
PARIET® 20 mg tablets

COMPOSITION

10mg: Each enteric-coated delayed release tablet contains 10 mg of rabeprazole sodium, equivalent to 9.42 mg rabeprazole (racemate).

20 mg: Each enteric-coated delayed release tablet contains 20 mg of rabeprazole sodium, equivalent to 18.85 mg rabeprazole (racemate).

PHARMACOLOGICAL CLASSIFICATION

A 11.4.3 Medicines acting on gastro-intestinal tract.

PHARMACOLOGICAL ACTION

Pharmacodynamics

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 drug is discontinued, secretory activity normalises over 2 to 3 days.

**Serum Gastrin Effects:**
In clinical studies patients were treated once daily with 10 or 20 mg rabeprazole sodium, for up to 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.

**Pharmacokinetics**
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<sub>max</sub>) 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.
Rabeprazole sodium is approximately 97 % bound to human plasma proteins.

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 is mainly urinary (90 %), with no unchanged drug 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.

In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤ 5 ml/min/1,73m²), the disposition of rabeprazole sodium was very similar to that in healthy volunteers.

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 Cmax increased by 60 % as compared to young healthy volunteers. However there was no evidence of rabeprazole sodium accumulation.

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.
CONTRA-INDICATIONS

PARIET is contra-indicated in:

- Patients with known hypersensitivity to rabeprazole sodium, substituted benzimidazoles or to any excipient used in the formulation.
- Pregnancy and lactation. (See also “PREGNANCY AND LACTATION”.)

INTERACTIONS

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

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 drugs are taken concomitantly with PARIET. In clinical trials, antacids were used concomitantly with the administration of PARIET and, in a specific drug-drug interaction study, no interaction with liquid antacids was observed. There was no clinically relevant interaction with food.

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 cyclosporin metabolism is similar to that observed for other proton pump inhibitors.

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 not studied, similar results are expected with other proton pump inhibitors. Therefore PPIs, including PARIET, should not be co-administered with atazanavir (See Special Precautions).

PREGNANCY AND LACTATION

Pregnancy

There are no data on the safety of rabeprazole sodium 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. (See also “CONTRA-INDICATIONS”.)

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. (See also “CONTRA-INDICATIONS”.)

DOSAGE AND DIRECTIONS FOR USE

Adults/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.

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.

Renal and hepatic impairment:
No dosage adjustment is necessary for patients with renal or hepatic impairment.
Caution is however advised when PARIET is first initiated in patients with severe hepatic dysfunction, refer “Side-Effects and Special Precautions”.

Children:

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

**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**

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 and post-marketing experience, by system organ class and frequency.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Common (&gt;1/100, &lt;1/10)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&gt;1/10 000, &lt;1/1000)</th>
<th>Very rare (&lt;1/10 000)</th>
<th>Not known</th>
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<tbody>
<tr>
<td>Infections and infestations</td>
<td>Infection</td>
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<td>Blood and the lymphatic system disorders</td>
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<td>Neutropenia</td>
<td>Leucopenia</td>
<td>Thrombocytopenia</td>
<td>Leucocytosis</td>
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<td>Immune system disorders</td>
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<td>Hyper-sensitivity</td>
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<td>Metabolism and nutrition disorders</td>
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<td>Anorexia</td>
<td>Hypomagnesemia</td>
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<td>Hyponatremia</td>
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<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Nervousness</td>
<td>Depression</td>
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<td>Confusion</td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
<td>Somnolence</td>
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<td>Eye disorders</td>
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<td>Visual disturbances</td>
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<td>Vascular disorders</td>
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<td>Peripheral oedema</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>Pharyngitis</td>
<td>Rhinitis</td>
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<td></td>
<td>Bronchitis</td>
<td>Sinusitis</td>
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<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Vomiting</td>
<td>Nausea</td>
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<td></td>
<td>Dyspepsia</td>
<td>Dry mouth</td>
<td>Eructation</td>
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<td>Gastritis</td>
<td>Stomatitis</td>
<td>Taste disturbances</td>
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<td>Hepato-biliary disorders</td>
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<td>Hepatitis</td>
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<td>Jaundice</td>
<td>Hepatic</td>
<td>Hepatic encephalopathy**</td>
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<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Erythema*</td>
<td>Pruritus</td>
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<td>Sweating</td>
<td>Bullous reactions*</td>
<td>Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)</td>
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<tr>
<td>Musculoskeletal, connective tissue and bone</td>
<td>Non-specific pain/back pain</td>
<td>Myalgia</td>
<td>Arthralgia</td>
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disorders

Renal and urinary disorders

Urine tract infection
Interstitial nephritis

Reproductive system and breast disorders

Gynaecomastia

General disorders and administration site conditions

Asthenia
Flu-like syndrome
Chest pain
Chills
Fever

Investigations

Increased hepatic enzymes**
Weight gain

* Erythema, bullous reactions and acute hypersensitivity reactions have usually resolved after discontinuation

** Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis.
   In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with PARIET is first initiated in such patients.

Special Precautions:
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.

Although 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, the prescriber is advised to exercise caution when treatment with PARIET is first initiated in patients with severe hepatic dysfunction.

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PARIET 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 PARIET.

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

Co-administration of atazanavir with PARIET is not recommended (See Interactions).

**KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT**

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 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.

**IDENTIFICATION**

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.

**PRESENTATION**

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

**STORAGE DIRECTIONS**

Store below 25 °C.

Protect from moisture. Do not store in the refrigerator.

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBERS**
South Africa:
10 mg: 33/11.4.3/0206
20 mg: 32/11.4.3/0614

Namibia
10 mg: 04/11.4.3/0248
20 mg: 04/21.8.2/0247

NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATES OF REGISTRATION

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