CLEAN FINAL PACKAGE INSERT

(Clean version submitted 18 August 2015)

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).

Inactives:

Calcium carboxymethylcellulose, carnauba wax, diacetylated monoglycerides, ethylcellulose, ferric oxide, hydroxypropyl cellulose, hypromellose phthalate, low-substituted hydroxypropyl cellulose, magnesium oxide, magnesium stearate, mannitol, talc, titanium dioxide.

Ferric oxide red is used as an excipient in all 10 mg tablets and ferric oxide yellow is used as an excipient in all 20 mg tablets.

PHARMACOLOGICAL CLASSIFICATION

A 11.4.3 Medicines acting on gastro-intestinal tract.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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.

Pharmacokinetic properties

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.

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 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.

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.

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.

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".)

WARNINGS AND SPECIAL PRECAUTIONS

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 Side 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 SIDE 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 INTERACTIONS).

Gastrointestinal infections

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

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

INTERACTIONS

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 Warnings and Special Precautions).

Methotrexate

Case reports suggest that 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.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

Pregnancy

Low foeto-placental transfer occurs in rats. PARIET is contra-indicated during pregnancy.

(See "CONTRA-INDICATIONS".)

Lactation

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 "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”.

Children:

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

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

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			Neutropenia Leucopenia Thrombocytopenia Leucocytosis		
Immune system disorders			Hypersensitivity (for example facial swelling, hypotension and dyspnoea)*		
Metabolism and nutrition disorders			Anorexia		Hypo-natraemia Hypo-magnesaemia
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	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbances		

	Abdominal pain Constipation Flatulence		Gastric glandular cysts		
Hepato-biliary disorders			Hepatitis Jaundice Hepatic encephalo-pathy**		
Skin and subcutaneous tissue disorders		Rash Erythema*	Pruritus Sweating Bullous reactions*	Erythema multi-forme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	
Musculoskeletal, connective tissue and bone disorders	Non-specific pain/back pain	Myalgia Leg cramps Arthralgia			
Renal and urinary disorders		Urinary 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		

There have been post-marketing reports of bone fractures.

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

** 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.

KNOWN SYMPTOMS OF OVERDOSAGE 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 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.

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

Primary packaging:

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

STORAGE DIRECTIONS

Aluminium/aluminium blister

Store below 25 ^{0}C.

Protect from moisture. Do not store in the refrigerator.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

10 mg: 33/11.4.3/0206

20 mg: 32/11.4.3/0614

NAME AND BUSINESS ADDESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

JANSSEN PHARMACEUTICA (Pty) Ltd

(Reg no. 1980/011122/07)

Building 6, Country Club Estate,

21 Woodlands Drive, Woodmead, 2191

Tel: +27 (11) 518 7000

www.janssen.co.za

DATE OF PUBLICATION OF THIS PACKAGE INSERT

Date of registration: 24 February 2000

Date of most recently revised package insert as approved by Council: 4 June 2015