PARIET PHARMACY 10MG GASTRO-RESISTANT TABLET

(Rabeprazole sodium)

PL 10555/0028

UK PAR

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LAY SUMMARY

The MHRA granted Eisai Limited a Marketing Authorisation (licence) for the medicinal product Pariet Pharmacy 10mg gastro-resistant tablet, on 25 January 2012. This product is licensed for sale in pharmacies, under the supervision of a pharmacist (legal status P).

Pariet Pharmacy 10mg gastro-resistant tablet contains the active ingredient rabeprazole sodium. This belongs to a group of medicines called ‘Proton Pump Inhibitors’ (PPIs). They work by lowering the amount of acid that the stomach produces. This medicine gives relief of heartburn and acid reflux (when acid and food from the stomach escapes into the food pipe).

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Pariet Pharmacy 10mg gastro-resistant tablet outweigh the risks; hence a Marketing Authorisation has been granted.
# PARIENT PHARMACY 10MG GASTRO-RESISTANT TABLET

**PL 10555/0028**

## SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted a Marketing Authorisation for the medicinal product Pariet Pharmacy 10mg gastro-resistant tablet (PL 10555/0028) to Eisai Limited on 25 January 2012. This product is licensed for sale in pharmacies, under the supervision of a pharmacist (legal status P) and indicated for the short term symptomatic treatment of gastro-oesophageal reflux-like symptoms (e.g. heartburn) in patients aged 18 and over.

This medicine contains the active ingredient rabeprazole sodium. Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, which 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.

This application was submitted as a simple abridged application according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Pariet 10mg gastro-resistant tablets (PL 10555/0010) approved on 08 May 1998 to the Marketing Authorisation Holder Eisai Limited. No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product.

This submission combined the application for a new product licence with a reclassification application to change the legal status of the product from a prescription-only medicine (POM) to a pharmacy product (P) for short-term symptomatic treatment of gastro-oesophageal reflux-like symptoms (e.g. heartburn) in patients aged 18 and over. Following a period of public consultation, the reclassification was discussed by the Commission on Human Medicines (CHM) on 15 to 16 July 2011, who advised in favour of the reclassification. This is supported by study data showing that the in-pharmacy assessment, including suitable training tools, ensures that the supply of the product is consistent with current guidelines. The final assessment and CHM advice are presented in Appendix 1.
**PHARMACEUTICAL ASSESSMENT**

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<td>COMPANY NAME:</td>
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<td>E.C. ARTICLE:</td>
<td>Article 10(c) of Directive 2001/83/EC</td>
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<td>LEGAL STATUS:</td>
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**1 INTRODUCTION**

This is a simple, informed consent application for Pariet Pharmacy 10mg gastro-resistant tablet, submitted under Article 10(c) of Directive 2001/83/EC and is linked to a parallel application to reclassify this duplicate license from POM to P (refer to annex 1). The application cross-refers to Pariet 10mg gastro-resistant tablets (PL 10555/0010) approved on 08 May 1998, to Eisai Limited.

The current application is considered valid.

**2 MARKETING AUTHORISATION APPLICATION (MAA)**

2.1 Name(s)

The proposed name of the product is Pariet Pharmacy 10mg gastro-resistant tablet. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Each tablet contains 10mg rabeprazole sodium and is packaged in aluminium/aluminium blister strips in pack sizes of 14 tablets.

The proposed shelf life (3 years) and storage conditions (Do not store above 25°C. Do not refrigerate) are consistent with the details registered for the cross-referenced product.

2.3 Legal status

The product is available as a Pharmacy (P) only medicine.

2.4 Marketing Authorisation Holder/Contact Persons/Company

The proposed Marketing Authorisation Holder is Eisai Ltd., European Knowledge Centre, Hatfield, Hertfordshire, AL10 9SN, UK.

The Qualified Person (QP) responsible for pharmacovigilance is stated and their CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with that registered for the reference product and evidence of compliance with current Good Manufacturing Practice has been provided.

2.6 Qualitative and quantitative composition

The composition is consistent with the details registered for the reference product.

2.7 Manufacturing process

The manufacturing process is consistent with the details registered for the reference product and the maximum batch size is stated.
2.8 **Finished product/shelf-life specification**
The finished product specifications are in line with the details registered for the reference product.

2.9 **Drug substance specification**
The drug substance specifications are consistent with the details registered for the cross-reference product.

2.10 **TSE Compliance**
None of the excipients contain materials of animal or human origin. None of the excipients are sourced from genetically modified organisms.

2.11 **Bioequivalence**
No bioequivalence data are required to support this informed consent application, as the proposed product is manufactured to the same formula utilising the same process as the reference product Pariet 10mg gastro-resistant tablets (PL 10555/0010).

3  **EXPERT REPORT**
The applicant has included a detailed pharmaceutical expert report, written by an appropriately qualified person.

4.  **PRODUCT NAME & APPEARANCE**
See 2.1 for details of the proposed product name. The appearance of the product is identical to that of the reference product.

5.  **SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)**
The proposed SmPC is consistent with the details registered for the reference product.

6.  **PATIENT INFORMATION LEAFLET (PIL)/LABELLING**

**PIL**
The patient information leaflet has been prepared in line with the details registered for the reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Carton and blister**
Mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements.

7.  **CONCLUSIONS**
The data submitted with this application is acceptable. The grant of a Marketing Authorisation is recommended.
NON-Clinical Assessment

As this application is identical to the reference product Pariet 10mg gastro-resistant tablets (PL 10555/0010), no new non-clinical data have been supplied with this application and none are required. A non-clinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As this application is for an identical version of an already authorised reference product, it is not expected that the environmental exposure to rabeprazole sodium will increase following the marketing approval of the proposed product.
CLINICAL ASSESSMENT

With the exception of the data for the assessment of the reclassification, no new clinical data were submitted for this application and none were required. A clinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has provided a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that the Marketing Authorisation Holder has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable risk management plan has been submitted for the reclassification of this product from POM to P.

The assessment of the clinical data submitted for the reclassification of this product is provided in Appendix 1.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for this application is consistent with that previously assessed for the reference product and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
With the exception of the data for the assessment of the reclassification, no new clinical data were submitted for this application and none were required.

The assessment of the clinical data submitted for the reclassification of this product is provided in Appendix 1.

SAFETY
No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the reference product. Extensive clinical experience with rabeprazole sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is therefore considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<td>1</td>
<td>The MHRA received the Marketing Authorisation Application on 19 March 2009.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 24 March 2009.</td>
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<td>3</td>
<td>Following assessment of the application the MHRA requested further information on 07 July 2010, 17 January 2011 and 01 June 2011</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information on 04 October 2010, 17 March 2011 and 18 July 2011</td>
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<tr>
<td>5</td>
<td>The application was determined on 25 January 2012.</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
PARIET PHARMACY 10mg gastro-resistant tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
10mg rabeprazole sodium, equivalent to 9.42mg rabeprazole
For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.
10mg: Pink, film coated biconvex tablet with 'E 241' printed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Short-term symptomatic treatment of gastro-oesophageal reflux – like symptoms (e.g. heartburn) in patients aged 18 and over.

4.2 Posology and method of administration
Adults/elderly:
The dosage is 10mg once daily in patients with heartburn. If symptomatic relief has not been achieved within two weeks or if continuous treatment for more than four weeks is required, then the patient should be referred to their doctor.

It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement of symptoms.

PARIET PHARMACY tablets should ideally 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 PHARMACY 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 4.4 Special Warnings and Precautions for Use of PARIET PHARMACY in the treatment of patients with severe hepatic impairment.

Children and adolescents under 18 years.
PARIET PHARMACY is not recommended for use in children and adolescents under 18 years, as there is no experience of its use in this group.

4.3 Contraindications
PARIET PHARMACY is contra-indicated in patients with known hypersensitivity to rabeprazole sodium, or to any excipient used in the formulation.
PARIET PHARMACY is contra-indicated in pregnancy and during breast feeding (see section 4.6).

4.4 Special warnings and precautions for use
Special warnings and precautions for patients taking non-prescription indigestion or heartburn remedies:
Patients should be referred to their doctor if:

• They have had to take an indigestion or heartburn remedy continuously for 4 or more weeks in order to control their symptoms
• They are aged over 55 years with new or recently changed symptoms
• If they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, pain on swallowing, persistent vomiting or vomiting with blood, epigastric mass, previous gastric ulcer or surgery, jaundice or any other significant medical condition (including hepatic and renal impairment).

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Patients aged over 55 years taking any “over the counter” (OTC, non-prescription) indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should not take another “acid suppressor” e.g. H2 antagonist or proton pump inhibitor concomitantly.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

Patients should avoid use prior to a urea breath test.

The Patient Information Leaflet will contain advice that the tablets will not provide immediate relief of symptoms.

A risk of cross-hypersensitivity reactions with other proton pump inhibitor or substituted benzimidazoles cannot be excluded.

Decreased gastric acidity, due to any means - including proton- pump inhibitors - increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid reducing drugs leads to a slightly increased risk of gastrointestinal infections such as salmonella, campylobacter or Clostridium difficile.

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

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 PHARMACY in the treatment of patients with severe hepatic dysfunction and patients should consult their doctor prior to initiating use. It is advised to exercise caution when treatment with PARIET PHARMACY is first initiated in such patients.

Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported since market authorisation. In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

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

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

Co-administration of atazanavir with PARIET PHARMACY is not recommended (see section 4.5).

Patients should not take PARIET PHARMACY as a preventative medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

As with many indigestion and heartburn remedies, rabeprazole may interact with other medications. Therefore, patients who are also taking other medications should first consult with either their pharmacist or doctor before taking rabeprazole.

Rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur. Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels.

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

Co-administration of atazanavir 300mg/ritonavir 100mg with omeprazole (40mg once daily) or atazanavir 400mg with lansoprazole (60mg 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 rabeprazole, should not be co-administered with atazanavir (see Section 4.4).
4.6 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 PHARMACY 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 PHARMACY should not be used during breast feeding.

4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that PARIET PHARMACY 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 commonly reported adverse drug reactions during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketed experience. Frequencies are defined as: common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

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1. Includes facial swelling, hypotension and dyspnoea
2. Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.
3. 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 (see section 4.4).

4.9 Overdose
Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60mg twice daily, or 160mg once daily. Effects are generally minimal, representative of 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 dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5 PHARMACOLOGICAL PROPERTIES
5.1 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 H$_2$ 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: In a study involving 24 healthy volunteers following administration of 10 and 20 mg rabeprazole for 7 days, the percent of time the gastric pH remained above 3 was 72% with 10 mg and 73% with 20 mg rabeprazole administration. In the same study oral administration of 10 mg or 20 mg rabeprazole resulted in an approximately 4 and 5-fold decrease in intragastric acidity (measured as 24-h median integrated acidity) respectively, relative to placebo.

Serum Gastrin Effects: In clinical studies patients were treated once daily with 10 or 20mg 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 20mg 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. Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with amoxicillin. Rabeprazole 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: PARIET PHARMACY 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 10 mg or 20mg dose. Peak plasma concentrations (C max) of rabeprazole and AUC are linear over the dose range of 10mg to 40mg. Absolute bioavailability of an oral 20mg 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. There was no clinically relevant interaction with food. 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: 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. In vitro studies with human liver microsomes indicated that rabeprazole 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 \textit{in vivo} status these findings indicate that no interaction is expected between rabeprazole and cyclosporin. 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 20mg $^{14}$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.

\textbf{Gender:} Data from two pharmacokinetic studies involving 42 male and 28 female healthy subjects who were administered a single dose of 10 mg rabeprazole tablets, show that female subjects had a 61.5 \% higher systemic exposure (AUC0-t) than males and a 48.8 \% higher peak plasma concentration of rabeprazole than males. However, clinical studies suggest no difference in safety and efficacy based on gender.

\textbf{Renal dysfunction:} In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq$5ml/min/1.73m$^2$), the disposition of rabeprazole was very similar to that in healthy volunteers. The AUC and the $C_{\text{max}}$ 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.

\textbf{Hepatic dysfunction:} Following a single 20mg 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 20mg dose daily for 7 days the AUC had increased to only 1.5-fold and the $C_{\text{max}}$ 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.

\textbf{Elderly:} Elimination of rabeprazole was somewhat decreased in the elderly. Following 7 days of daily dosing with 20mg of rabeprazole sodium, the AUC approximately doubled, the $C_{\text{max}}$ increased by 60\% and $t_{1/2}$ increased by approximately 30\% as compared to young healthy volunteers. However there was no evidence of rabeprazole accumulation.

\textbf{CYP2C19 Polymorphism:} Following a 20mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and $t_{1/2}$ which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolisers whilst $C_{\text{max}}$ had increased by only 40\%.

5.3 \textbf{Preclinical safety data}
Non-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 \textit{in vivo} micronucleus and \textit{in vivo} and \textit{in vitro} DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

6 \textbf{PHARMACEUTICAL PARTICULARS}

6.1 \textbf{List of excipients}
\textbf{Core tablet:}
- Mannitol
- Magnesium oxide
- Low-substituted hyprolose,
- Hyprosole
- Magnesium stearate

\textbf{Undercoating:}
- Ethylcellulose,
- Magnesium oxide
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 25°C. Do not refrigerate

6.5 Nature and contents of container
Blister strips (aluminium/aluminium)
Pack size: 14 tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Eisai Ltd., European Knowledge Centre,
Hatfield, Hertfordshire AL10 9SN, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)
PL 10555/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/01/2012

10 DATE OF REVISION OF THE TEXT
25/01/2012
PATIENT INFORMATION LEAFLET

Pariet® Pharmacy
Rabeprazole sodium
10 mg gastro-resistant tablets

In this leaflet:
1. What Pariet Pharmacy is and what it is used for
2. Before you take Pariet Pharmacy
3. How to take Pariet Pharmacy
4. Possible side effects
5. How to store Pariet Pharmacy
6. Further information

1. What Pariet Pharmacy is and what it is used for
Pariet Pharmacy tablets contain the active ingredient rabeprazole sodium. This belongs to a group of medicines called Proton Pump Inhibitors (PPIs). They work by lowering the amount of acid that your stomach produces.

2. Before you take Pariet Pharmacy
Do not take Pariet Pharmacy if:
- You are allergic (hypersensitive) to rabeprazole sodium, or any of the other ingredients of Pariet Pharmacy (listed in Section 6 below).
- You are pregnant or think that you are pregnant.
- You are breastfeeding.

Pariet Pharmacy tablets give relief of heartburn and acid reflux (when acid and food from your stomach escape into your food pipe).

Ask your doctor before you take this medicine if:
- You have unintentionally lost weight, anemia, bleeding from stomach, difficulty or pain on swallowing, persistent vomiting or vomit blood, a lump in your stomach area, jaundice or have previously had a gastric ulcer or stomach surgery.
- You are 55 years or older with symptoms that are new or recently changed or if you need to take treatment for your symptoms on a daily basis.

Children
Pariet Pharmacy should not be used in children or teenagers who are under the age of 18 years.

Take special care with Pariet Pharmacy
Check with your pharmacist before taking Pariet Pharmacy if:
- You are allergic to other proton pump inhibitor medicines.
- You have a stomach tumour.
- You have ever had liver problems.
- If you are taking atazanavir – for HIV infection.
- If you experience severe (watery or bloody) diarrhoea with symptoms such as fever, abdominal pain or tenderness, stop taking Pariet Pharmacy and see a doctor straight away.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pariet Pharmacy.

Using other medicines
Please tell your pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines. In particular, tell your pharmacist if you are taking any of the following medicines:
- Ketoconazole or itraconazole – used to treat infections caused by a fungus. Pariet Pharmacy may lower the amount of this type of medicine in your blood. Your doctor may need to adjust your dose.
- Azithromycin – for HIV infection. Pariet Pharmacy may lower the level of azithromycin in your blood and they should not be used together.
- You should not take other medicines to control stomach acid (eg, either PPIs or tablets called H2 blockers) at the same time as this medicine.
- Tell your doctor about any treatments you are taking for heartburn or indigestion (if you are going to have a test called an endoscopy, this is a test that looks inside the foodpipe). Avoid using Pariet Pharmacy if you are going to have a sensor test.
- Pregnancy and breastfeeding
- Do not use if you are pregnant or think you may be pregnant.
- Do not use if you are breastfeeding or planning to breast feed.

Ask your pharmacist for advice before taking any medicine during pregnancy or while breastfeeding.

Taking Pariet Pharmacy with food and drink
Having your tablets with or after food does not affect how Pariet Pharmacy works.

Driving and using machines
You may feel sleepy while taking Pariet Pharmacy. In this happens, do not drive or use any tools or machines.

Special advice for people taking medicines for indigestion or heartburn without a prescription
You should talk to your pharmacist or doctor if:
- You need to take medicines for indigestion or heartburn for more than 4 weeks or more to control your symptoms.
- You have lost weight without trying to, you have been told you are anemic, or you have had bleeding from your stomach or have black stools.
- You have difficulty swallowing or it is painful.
- You are being sick a lot or there is blood in your sick.
- You have noticed a lump in your stomach.
- You have had stomach ulcers in the past or surgery for ulcers.
- You have yellowing of the skin (jaundice) or any other serious illness.

MHRA PAR-Pariet Pharmacy 10mg gastro-resistant tablets (PL 10555/0028) 18
3. How to take Pariet Pharmacy

Always take Pariet Pharmacy exactly as this leaflet tells you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- Only remove a tablet from the blister strip when it is time to take your medicine.
- Swallow your tablets whole, with a drink of water. Do not chew or crush the tablets.
- Take one Pariet Pharmacy 10 mg tablet once a day for up to 2 weeks until your symptoms are completely gone. If you still have symptoms after taking Pariet Pharmacy every day for 4 weeks you should talk to your doctor.
- You may not get relief of your symptoms with the first dose of Pariet Pharmacy.

If you take more Pariet Pharmacy than you should
- If you take more Pariet Pharmacy than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you.

If you forget to take Pariet Pharmacy
- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual.
- Do not take a double dose (two doses at the same time) to make up for a forgotten dose.
- If you have any further questions on the use of this product, ask your pharmacist.

4. Possible side effects

Like all medicines, Pariet Pharmacy may sometimes cause side effects, although not everybody gets them.

The side effects are usually mild and improve without you having to stop taking this medicine.

Stop taking Pariet Pharmacy and see a doctor straight away if you notice any of the following side effects - you may need urgent medical treatment:
- Allergic reactions - the signs may include: sudden swelling of your face, difficulty breathing or low blood pressure which may cause fainting or collapse.
- Frequent infections, such as a sore throat or high temperature (fever), or ulcers in your mouth or throat.
- Bruising or bleeding easily.
- These side effects are rare (affect less than 1 in 1,000 people).

Other possible side effects:

Common (affect less than 1 in 10 people)
- Infections.
- Difficulty sleeping.
- Headache or feeling dizzy.
- Cough, runny nose or sore throat (pharyngitis).
- Effects on your stomach or gut such as stomach pain, diarrhea, wind (flatulence), feeling sick (nausea), being sick (vomiting) or constipation.
- Non-specific pain or back pain.
- Weakness or flu-like symptoms.

Uncommon (affect less than 1 in 100 people)
- Feeling nervous or drowsy.
- Chest infection (bronchitis).
- Painful and blocked sinuses (sinusitis).
- Dry mouth.
- Indigestion or belching.
- Skin rash or redness.
- Muscle, leg or joint pain.

Other possible side effects (unknown frequency)
- Bladder infection (urinary tract infection).
- Chest pain.
- Chills or fever.
- Changes in how your liver is working (shown in blood tests).
- Rare (affect less than 1 in 1,000 people)
- Anaemia.
- Depression.
- Hypersensitivity.
- Visual disturbance.
- Sore mouth (stomatitis) or taste disturbance.
- Upset stomach.
- Liver problems including yellowing of your skin and whites of your eyes (jaundice).
- Itchy rash or blistering skin.
- Sweating.
- Kidney problems.
- Weight gain.
- Changes in white blood cells (shown in blood tests).
- Reduction in platelets.

Very rare (affect less than 1 in 10,000 people)
- Severe skin blistering, or soreness or ulcers in your mouth and throat.

Do not be concerned by this list of side effects. You may not get any of them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
5. How to store Pariet Pharmacy

Keep out of the reach and sight of children.
Do not store this medicine above 25°C.
Do not refrigerate.
Do not use Pariet Pharmacy after the expiry date which is stated on the carton and blister foil. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines that are no longer required. These measures will help to protect the environment.

6. Further Information

What Pariet Pharmacy contains

Each Pariet Pharmacy 10 mg tablet contains 10 mg of the active substance rabeprazole sodium.

The other ingredients it contains are: mannnitol, magnesium oxide, low-substituted hydroxyproline, hydroxyproline, magnesium stearate, ethylcellulose, hypromellose phthalate, diacetylated monoglycerides, talc, titanium dioxide (E171), red iron oxide (E172), Carnauba wax and ink (white shellac, black iron oxide (E172)), dehydrated ethyl alcohol, 1-butanol.

What Pariet Pharmacy looks like and contents of the pack

Pariet Pharmacy 10 mg gastro-resistant tablet is a pink, film coated biconvex tablet with 'E241' printed on one side.

The tablets are packed in blister strips and come in pack sizes that contain: 14 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Eisai Ltd., European Knowledge Centre
Mosquito Way,
Hatfield,
Herts,
AL10 9SN
UK

Manufacturer:

Eisai Manufacturing Ltd, European Knowledge, Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN United Kingdom.

Pariet Pharmacy bulk tablets are manufactured for Eisai Ltd. by: Eisai Co. Ltd., (Misato Plant),
950 Oaza Hikko, Misato-cho, Kodama-gun,
Saitama Prefecture 367-0198, Japan.

This leaflet was last approved in 01/2012.
LABELLING

Carton:

Pariet ® Pharmacy 10mg
Gastro Resistant Tablet
RAPEBRAZOLE SODIUM

Each gastro-resistant tablet contains the active ingredient rabeprazole sodium 10mg. Also includes mannitol.

Keep out of the sight and reach of children
Do not store above 25°C. Do not refrigerate.

Pariet Pharmacy 10mg is a short-term treatment for the relief of heartburn and acid reflux. They work by preventing the stomach producing too much acid which can cause acid reflux and heartburn.

PLEASE READ THE ENCLOSED LEAFLET CAREFULLY BEFORE TAKING THESE TABLETS.

The medication may not bring immediate relief it may take 2-3 days to control symptoms.

HOW TO TAKE
Swallow these tablets whole with plenty of water. Do not chew or crush the tablets.
Swallow these tablets whole.
Adults 18 years and over: Take one tablet daily.

DO NOT EXCEED THE STATED DOSE.

DO NOT TAKE
Do not give to children under 18 years of age.
• If you are allergic to rabeprazole sodium or any of the other ingredients.
• If you are pregnant or are breast-feeding.

CONSULT YOUR DOCTOR:
• If you have no symptom relief within 2 weeks.
• If you need to take Pariet Pharmacy 10mg for more than 4 weeks to control your symptoms.
• If you have unintentionally lost weight, anaemia, bleeding of the stomach, difficulty or pain on swallowing, persistent vomiting or vomiting blood, a lump in your stomach area, jaundice or have previously had a gastric ulcer or stomach surgery.
• If you are 55 years or older with symptoms that are new or recently changed or if you need to take treatment for your symptoms on a daily basis.

14 Tablets
PLEASE READ THE ENCLOSED LEAFLET CAREFULLY BEFORE TAKING THESE TABLETS
KEEP OUT OF SIGHT AND REACH OF CHILDREN

EML cannot accept responsibility for any errors in the Braille after artwork is approved. Extreme care is taken in the setting of the Braille, however the reviewer must take final responsibility for it’s accuracy. Braille is set to Marburg Medium format unless specified otherwise. Approval of this proof signifies approval of the Braille text and specification.
Blister:
Appendix 1: Final assessment of the reclassification from POM to P and CHM advice (July 2011).

1. EXECUTIVE SUMMARY

This is an abridged reclassification application submitted by Eisai Limited requesting Pharmacy (P) availability for Pariet Pharmacy 10mg gastro-resistant tablets (henceforth known as Pariet Pharmacy), an oral, enteric-coated tablet product containing 10mg rabeprazole sodium (equivalent to 9.42mg rabeprazole). The product is currently a Prescription Only Medicine (POM). The Marketing Authorisation Holder (MAH) proposes the following indication for the reclassified pharmacy product:

Short-term symptomatic treatment of gastro-oesophageal reflux-like symptoms (e.g. heartburn) in patients aged 18 and over.

The following conditions are proposed for P supply of Pariet Pharmacy:

- tablets for oral administration
- short-term symptomatic treatment of gastro-oesophageal reflux-like symptoms
- adults aged 18 years and over
- maximum strength: 10mg rabeprazole sodium (equivalent to 9.42mg rabeprazole)
- maximum dose: 10mg
- maximum daily dose: 10mg
- maximum pack size: 14 tablets

Data from clinical trials support the reclassification of rabeprazole 10mg. In endoscopically negative subjects with moderately severe chronic Gastro-Oesophageal Reflux Disease (GORD) symptoms, rabeprazole 10mg once-daily showed significantly greater symptomatic relief than placebo. In common with the other reclassified Proton Pump Inhibitors (PPIs), rabeprazole is a well-tolerated drug with a low incidence of adverse effects. Clinical trials data indicate that the most common adverse drug reactions were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The most important consideration in the reclassification of rabeprazole relates to the potential ‘indirect danger’ of acid-suppressing drugs to mask the symptoms of gastric or oesophageal malignancy. In this regard it is important that potential consumers and pharmacists are reminded of symptoms and signs that increase the possibility of an underlying malignancy as the cause of presentation (alarm signs: GI bleeding, difficulty swallowing, unintentional weight loss, abdominal swelling and persistent vomiting). This is achieved through product information, training and guidance provided to the pharmacist and pharmacy staff, in particular, through evaluation of criteria for patient referral if any of the cardinal warning signs are encountered.

The PIL and packaging make it clear that this product is not for use in children or adolescents under the age of 18 years. Through wider availability of rabeprazole, pharmacists will have an important, additional opportunity to give advice; including lifestyle advice, for the treatment of heartburn.

Patients are very familiar with the self-diagnosis of heartburn and other reflux symptoms. There are two other PPIs already reclassified: omeprazole and pantoprazole.
and a range of other preparations available, including numerous H$_2$-receptor antagonists (H$_2$RAs), alginates and antacid medications.

The Commission is asked to consider whether, in respect of the conditions described above, rabeprazole sodium 10mg tablets may safely be sold or supplied without prescription, under the supervision of pharmacist.

2. INTRODUCTION

Eisai Ltd has submitted an abridged reclassification application to obtain authorisation to market Pariet Pharmacy tablets, containing rabeprazole sodium 10mg. The proposed product will be indicated for the short-term symptomatic treatment of gastro-oesophageal reflux-like symptoms (e.g. heartburn) in patients aged 18 and over. The applicant wishes to license and market a 14 tablet pack, sufficient for 14 days continual treatment, based on a maximum daily dose of 10mg.

Assessor’s comments:

The requirements for the duplicate licence, abridged to the Pariet 10mg prescription product, have been met by the applicant and therefore this paper will focus on the change in legal status from POM to P.

3. BACKGROUND AND LICENSING HISTORY

Pariet Pharmacy is an oral, enteric-coated tablet product containing the sodium salt of rabeprazole. 10mg of rabeprazole sodium is equivalent to 9.42mg of rabeprazole. The tablets are an identical formulation to the reference product against which this abridged reclassification application is made; Pariet 10mg tablets (PL 10555/0010).

The Pariet 10mg and 20mg products were first authorised in the UK in 1998 as Prescription Only Medicines, approved for the treatment of:

- active duodenal ulcer;
- active benign gastric ulcer;
- symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD).

Subsequent variations added the following indications to the SPC of the prescription product:

- Gastro-Oesophageal Reflux Disease Long-term Management (GORD Maintenance);
- Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD);
- Zollinger-Ellison Syndrome.

The POM product is also licensed for use in combination with appropriate antibacterial therapy for the eradication of Helicobacter Pylori in H. Pylori positive patients with peptic ulcer disease.

Rabeprazole 10mg and 20mg products received their first marketing authorisation approvals in Japan on 14 October 1997. The first European approval for both the 10mg and 20mg tablet products was in the UK, 8th May 1998. Rabeprazole has been approved...
for marketing in 99 countries. This is the first reclassification application for this drug in the UK. The applicant proposes a revised P indication as follows:

Symptomatic treatment of gastro-oesophageal reflux-like symptoms (e.g. heartburn) in patients aged 18 years and over

The proposed indication is restricted when compared to the indications of the POM product.

Two other oral PPIs can already be purchased over-the-counter (OTC) in the UK: omeprazole and pantoprazole. Omeprazole is available as a P status product for the relief of reflux-like symptoms (available since January 2004). Additionally pantoprazole has recently been approved for use as a non-prescription product (short-term treatment of reflux symptoms) using the centralised application procedure and is widely available across the European Union without prescription (approved June 2009). Lanzoprazole is also available in Sweden as a non-prescription drug. Worldwide, rabeprazole is already available in Australia as a non-prescription product (January 2011). The proposed OTC UK indications are in line with other PPIs already reclassified in the UK and throughout Europe.

There are a wide variety of other OTC drugs used for the relief of heartburn including H₂-antagonists, such as cimetidine, ranitidine, and famotidine. Algicrates (e.g. Gaviscon), bismuth subsalicylate (e.g. Pepto-Bismol) and a plethora of antacids products, containing aluminium or magnesium salts designed to directly neutralise stomach acid.

4. PROPOSED TERMS OF DEREGULATION

The proposed indication for the pharmacy product is the short-term symptomatic treatment of gastro-oesophageal reflux-like symptoms (e.g. heartburn) in patients aged 18 and over. The proposed posology is one 10mg tablet daily. Product information informs patients that it may be necessary to take the tablets for 2-3 days to improve symptoms and if symptomatic control has not been achieved within two weeks, the patient should be referred to their doctor for further investigation. In line with OTC pantoprazole and omeprazole, patients requiring more than four weeks continuous use should also be referred to their doctor.

To facilitate the above restrictions, the proposed pack size is 14 tablets, sufficient for two weeks continual use. Pharmacists therefore have the opportunity to provide advice, and where necessary refer patients, on more than one occasion.

According to their respective SPCs, the current UK innovator POM products Pariet (10mg and 20mg) can be taken in doses of up to 120mg per day (60mg twice daily) for Zollinger-Ellison Syndrome, though doses of 20mg per day are more typical.

The EC Directive on the Community Code relating to Medicinal Products for Human Use (2001/83/EC, as amended) classifies medicines into those subject to medical prescription and those not subject to prescription control. These criteria have been incorporated into section 58A (2) of the Medicines Act 1968. Prescription control is required for medicines which meet the following criteria:
is likely to present a direct or indirect danger to human health, even when used correctly, if utilised without supervision of a doctor or dentist; or
is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health; or
contains a substance or preparation of substances of which the activity requires, or the side-effects require, further investigation; or
is normally prescribed by a doctor of dentist for parenteral administration.

This reclassification assessment is directed at the first three of these criteria; the last criterion is not relevant since the product is not to be administered parenterally.

5. PHARMACEUTICAL ASSESSMENT OF SUITABILITY FOR PHARMACY AVAILABILITY

5.1 Product name
The applicant wishes to delete the prescription trade name Pariet 10mg gastro-resistant tablets from the duplicate licence and introduce a replacement name for the reclassified pharmacy product; Pariet Pharmacy 10mg gastro-resistant tablets. The proposed name is acceptable as the addition of the word pharmacy describes the legal status and sufficiently distinguishes the P product from the POM product. There are other OTC products with Pharmacy legal status that also have pharmacy included as part of their product name.

5.2 Pack size
A 14 tablet pack size is the only pack size proposed for the pharmacy product. Based on a posology of 1x 10mg tablet daily (maximum dose), each pack represents no more than 14 days treatment. If symptomatic control has not been achieved within two weeks (1 pack of 14 tablets) or more than four weeks (2x packs of 14 tablets) continuous treatment is required to control symptoms, the patient should be referred to their physician. A smaller pack of 14 tablets (as opposed to a single pack of 28 tablets) has the advantage of getting the patient back into the pharmacy for the additional, second pack. Increased contact with the pharmacist is advantageous as the success of the first pack and the requirement for a second pack can be assessed and referral advised where appropriate. However the pharmacist would have to be sure that the returning patient is not attempting to purchase a third or fourth continual pack; a difficult task given the number patients visiting a typical pharmacy each day. There is also nothing preventing the patient purchasing additional packs from other pharmacies.

The smaller pack has the advantage of reducing the amount of medicine available in the patient’s home, though this must be balanced with the inconvenience of having to return to the pharmacy for additional packs. On balance, the 14 tablet pack size is appropriate for a product of this type. The pack size is in line with other OTC PPIs: pantoprazole 7 & 14 tablets packs available, omeprazole 7, 14 and 28 tablet packs available.

The current marketed POM pack is 28 tablets, (2 blister strips of 14 tablets) though the SPC contains authorisation for packs containing up to 120 tablets. The P product pack
size of 14 contains a single blister strip of 14 tablets and is in line with current blister packaging specifications for the POM product.

5.3 Product information

The applicant has provided a mock-up version of the intended patient information leaflet (see Annex II). Document M1-3-4-consult-with-target-patient-groups-bridging-report RECLASS.pdf provided bridging data to the pharmacy product leaflet which was based on the POM product. As a result of discussions with the MAH, this was not considered appropriate for the reclassified product and a full user test has been provided.

Reference to Braille text is present on the carton and complies with the Braille provisions contained in Article 56(a) of Directive 2001/83 EC, as amended. The application also includes a full colour mock-up of the carton labelling with the placement and content of the Braille text which is approvable.

A training protocol has been proposed by the applicant (refer to section 10 of this report).

Pharmaceutical points relating to the proposed SPC, labelling and patient information leaflet are included in section 9 of this report.

6. MEDICAL ASSESSMENT OF SUITABILITY FOR PHARMACY AVAILABILITY

6.1 Pharmacodynamics

Currently available PPIs are all membrane permeable weak bases that concentrate in the acid environment of the actively secreting parietal cell as pro-drugs, before acid-catalysed conversion into active derivatives. These then bind, by covalent bridges, to cysteine residues on parts of the H⁺/K⁺ ATPase enzyme, thereby blocking the functioning of this ‘proton pump’ for sustained periods.

Rabeprazole shows high accumulation and fast conversion to active forms. An in vitro gastric vesicle model comparing speed of H⁺/K⁺ ATPase inhibition with PPIs confirmed faster inhibition with rabeprazole. This potential for early inhibition of acid secretion was reflected in a volunteer study comparing intragastric pH in the 24 hours post-dosing with rabeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg or two dosage forms of omeprazole 20mg (capsule and multiple unit pellet system (MUPS) tablet). Rabeprazole produced the highest median 24 hour pH (pH 3.4) and the greatest proportion of time at pH >4 compared with the other PPIs (p<0.04) in the first 24 hours. Other studies have established that inhibition of basal and food stimulated acid secretion 25 hours after the first dose of rabeprazole sodium are 69% and 82% respectively and the duration of inhibition lasts up to 48 hours.

Rabeprazole’s high pKa relative to other PPIs (5 vs. approximately 4) makes it less dependent on low pH for its activation and so subsequent doses can continue to bind and inhibit the pump at higher pH levels, resulting in early sustained acid suppression compared with other proton pump inhibitors.
Studies have demonstrated that pantoprazole, omeprazole and esomeprazole require several days of repeated administration to build to maximum effect, whereas acid inhibitory effects with rabeprazole and lansoprazole are closer to their maximum effects after initial dosing. The inhibitory effect of rabeprazole sodium on acid secretion increases only 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.

Assessor’s comments:

There are slight differences between the pharmacokinetic and pharmacodynamic properties of different PPIs. Rabeprazole - which is a less acid-stable PPI than omeprazole, pantoprazole and lansoprazole - has a faster acid inhibition in vitro.

In a healthy volunteer study by Pantoflickova et al. a 20mg single dose of rabeprazole significantly increased intragastric pH, which was maintained over night and also significantly increased the amount of time at gastric pH ≥4 – a pH, which is necessary for healing of gastric and duodenal ulcer and erosive oesophagitis. The onset of action was within 2 hours. The authors stated that in this exploratory study rabeprazole provided greater acid control than other PPIs (such as omeprazole, lansoprazole, pantoprazole).

In clinical efficacy studies however, there has been no difference found between different PPIs in the healing rates of erosive oesophagitis. Different PPIs are indeed used interchangeably in clinical practice.

The above studies mainly used 20mg rabeprazole and not 10mg, which is the proposed dose for pharmacy availability. Clinical efficacy assessed as symptomatic relief of GORD was not reported. Therefore, the relevance of the above findings to the proposed OTC indication is unclear.

Other PPIs already OTC are indicated for the short-term treatment of GORD symptoms. The indication of rabeprazole is in line with these PPIs (omeprazole and pantoprazole). The MAH has amended the SPC following previous RFI letters.

6.2 Pharmacokinetics

All proton pump inhibitors are subject to hepatic metabolism by the cytochrome P\textsubscript{450} (CYP450) isoenzymes; CYP2C19 and CYP3A4. However rabeprazole sodium is unique in that a non-enzymatic pathway (involving reduction to rabeprazole thioether with subsequent renal elimination of metabolites) predominates and both CYP450 isoenzymes contribute in a limited way to overall metabolism.

The implications of this are twofold:

1. Genetic polymorphism of CYP2C19 has relatively little impact on rabeprazole pharmacokinetics.
2. Rabeprazole has low potential to cause drug interactions based on CYP450 effects, in contrast to e.g. omeprazole which has the potential to inhibit the hepatic elimination of several drugs.

Assessor’s comments:

In vitro data show that rabeprazole thioether has an inhibition potential of CYP2C19 similar to omeprazole. However, the clinical relevance of this finding is unclear.

The interaction potential of PPIs with clopidogrel has recently been under scrutiny as clopidogrel is a drug, which is activated via CYP2C19. The current regulatory advice is that concomitant use of clopidogrel and omeprazole should be discouraged.

6.3 Efficacy

The current POM indication and posology include the following:

**Indication:** Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD)

**Posology:** 10mg 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 10mg once daily when needed.

The proposed P indication and posology are:

**Indication:** Short-term symptomatic treatment of reflux-like symptoms (e.g., heartburn) in sufferers aged 18 and over.

**Posology:** The dosage is 10mg once daily in patients with heartburn. If symptom control has not been achieved within two weeks or if continuous treatment for more than four weeks is required, then the patient should be referred to their doctor.

The proposed pharmacy setting for rabeprazole use in GORD patients mirrors that currently in General Practitioner-led primary care, in that presenting patients will generally have troublesome heartburn that has not been adequately treated by antacids, antacid/alginate mixtures or H2RAs (if these have been tried). The current NHS Clinical Knowledge Summary (CKS, formerly Prodigy guideline) and NICE guidelines for dyspepsia do not recommend endoscopy for patients without ‘alarm symptoms’ which might suggest serious underlying disease. The guidelines now agree that a course of treatment with a PPI should be tried empirically. The key differences with the P product are that the course is short-term and for less severe symptoms, at a lower dose of rabeprazole with the option of referral to a doctor if appropriate.

Severity of heartburn has an imperfect correlation with endoscopic appearance, but response to a PPI suggests an important role for oesophageal acid exposure in the genesis of symptoms. The acute efficacy of rabeprazole in treating symptoms will likewise not distinguish reliably between those individuals with no or mild erosions (often termed endoscopy negative reflux disease or (ENRD)) and those with erosive
disease. However 20mg doses of rabeprazole are often required for periods of 4-8 weeks to heal erosions and in the absence of healing, poor control and frequent symptomatic relapses are to be expected. The totality of evidence suggests that ‘on demand’ maintenance of symptom control is not a successful symptomatic strategy in erosive disease.

Assessor’s comments:

Erosive disease requires long-term treatment with higher doses. This supports the proposed posology that if symptomatic relief has not been achieved within two weeks or if continuous treatment for more than four weeks is required, the patient should be referred to their doctor.

The great majority of people with heartburn in the community will have ENRD and it is partly for this reason that guidelines propose a symptom-led approach to heartburn and associated symptoms. The likely population for self-medication with rabeprazole 10mg is thus essentially similar to that currently recommended to take 10mg in the prescription label, i.e. those with symptomatic GORD, but without oesophagitis. The absence of oesophagitis has to be assumed in both settings, but revisited and possibly investigated if the sufferer fails to respond adequately to initial treatment or fails to be controlled by short-term dosing to maintain symptom control.

Assessor’s comments:

The National Institute for health and Clinical Excellence (NICE) guideline (published in 2004) states that approximately 40% of the adult population suffers from dyspepsia. The guideline defines dyspepsia as a spectrum of usually intermittent upper gastrointestinal (GI) symptoms, including heartburn, epigastric pain or acid regurgitation with or without bloating, nausea or vomiting. The clinical entity of uninvestigated dyspepsia is recognised and distinguished from the three main other categories, which are arising from investigation: gastro-oesophageal reflux disease, peptic ulcer disease and non-ulcer dyspepsia.

The symptoms of dyspepsia affect the quality of life of the majority of patients. Although lifestyle advice can help to avoid triggering dyspepsia, evidence on its long-term impact is lacking. It is therefore inappropriate to withhold treatment on lifestyle grounds.

In most patients without alarm signs (GI bleeding, difficulty swallowing, unintentional weight loss, abdominal swelling and persistent vomiting) it is appropriate to manage symptoms without a formal diagnosis.

The NICE guideline recommends initial empirical treatment with a PPI using full dose. Subsequent treatment with a PPI can be tailored to the consequence of the initial trial therapy, but periodic review should empower patients to continue, reduce or cease therapy.

The NICE guideline does not recommend routine endoscopic investigation of patients without alarm signs. However, in patients over 55 years, endoscopy should be considered when symptoms persist despite treatment and patients have certain factors
(such as previous gastric ulcer, continuous NSAID therapy, risk of gastric cancer). This advice is reflected in the SPC, which advises referral of patients aged over 55 years with new or recently changed symptoms.

The MAH considers that the proposed OTC indication reflects the existing approved indication of symptomatic GORD. The acute efficacy of PPIs on heartburn is well established. The MAH reviewed unpublished data generated on 10mg rabeprazole to support symptomatic treatment in an ‘OTC’ indication in the United States. The MAH considers that symptomatic treatment in an OTC setting appropriate.

6.3.1 Efficacy of Rabeprazole for Acute Treatment of Symptomatic GORD

The MAH sponsored several studies in symptomatic non-erosive GORD performed in the US, one of which was essentially a ‘dose ranging’ study for the POM indication. In study RAB-USA-2 (subsequently published), subjects were treated in a double-blind, randomised fashion with rabeprazole 10mg, rabeprazole 20mg, or placebo once daily for 4 weeks. The percentages of subjects with complete relief of heartburn at week 4 were 29.3% for rabeprazole 10mg daily, 28.3% for rabeprazole 20mg daily, and 3.4% for placebo (p<0.001, rabeprazole vs. placebo). In this study, median time to the first 24-hour heartburn-free period was 2.5 and 4.5 days with rabeprazole 10 and 20mg daily doses respectively, vs. 21.5 days with placebo (p≤0.004).

Assessor’s comments:

This study included endoscopically negative patients with moderately severe GORD symptoms who were treated over a 4-week period. The primary efficacy endpoint was the median time for patients to achieve their first 24-hour interval without heartburn. The primary endpoint and the treatment duration of this study correlates with the proposed indication and treatment duration for pharmacy supply. Although patients’ conditions were confirmed with endoscopy, which will not be the case in the OTC setting, empirical treatment of GORD symptoms is accepted clinical practice (See recommendations of NICE guideline above).

This study found that the median time to first heartburn free period is 2.5 days. Therefore Section 4.2 of the SPC includes the following information:

“It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement of symptoms”.

This important consideration is reflected in the proposed product information.

A recent Cochrane Collaboration Review examined randomised controlled trials which focused on symptomatic outcome after short-term treatment for GORD using proton pump inhibitors, H2RAs or prokinetic agents. Studies were included that classified participants as comprising an empirical treatment group (i.e. no endoscopy used in treatment allocation) or an endoscopy negative reflux disease [ENRD] group (no endoscopic signs of erosive oesophagitis). This review (31 trials including 9457 subjects) found that in the short term, PPIs relieve heartburn better than H2RAs in patients who are treated without specific diagnostic testing and, although the difference was smaller, also in patients with GORD who have a normal upper endoscopy. This
latter finding is not surprising since it is well recognised that reflux symptoms in ENRD are not always driven exclusively by oesophageal acid exposure and therefore response rates to all anti-secretory drugs may be lower. In turn this makes differences based on potency of inhibition more difficult to detect.

**Assessor’s comments:**

The review included 15 studies where heartburn was treated empirically. There were no studies with rabeprazole included in the empirical treatment group. Short-term treatment was considered as one to twelve weeks.

The MAH has recently conducted two large randomised placebo-controlled studies of essentially identical design in a total in 1,200 subjects (600 completed each study) with frequent heartburn (suffering more than 2 days per week) responsive in some degree to antacids or H2RAs. Following a 1-week single blind placebo run-in phase (during which frequency of suffering was confirmed), sufferers entered a 2 week randomised double blind treatment phase at the end of which they were followed for 1 week on single-blind placebo.

The primary objective in both studies was to examine the efficacy of 10mg rabeprazole (vs. placebo) in producing complete heartburn relief in the first 24 hours of the treatment phase. Secondary endpoints included the effect of rabeprazole on frequency of daytime and night time heartburn (i.e. days or nights with event) as well as on secondary reflux symptoms of regurgitation and belching.

- The proportion of sufferers experiencing complete heartburn relief within 24 hours was significantly greater for rabeprazole 10mg in both studies (in one study $p<0.001$ for both intention to treat [ITT] and per protocol [PP] analyses; in the other study this difference was only significant on the PP analysis until adjustment for baseline number of episodes, when both PP and ITT analyses were significant $p<0.001$). This difference in complete heartburn relief was maintained over the 14 days in both studies. The range of proportions heartburn-free with rabeprazole and placebo over the 14 days were 51-63% and 34-44% respectively in one study and 36-58% and 26-39% respectively in the other.
- Rabeprazole 10mg also reduced the frequency of both daytime and night time heartburn (i.e. days with the event) and rabeprazole 10mg produced complete freedom from heartburn in both periods in a greater proportion of subjects ($p<0.001$) in both studies.
- Improvement of regurgitation and belching was greater with rabeprazole than placebo, but reached statistical significance only for belching in one study.

**Assessor’s comments:**

Patients were treated empirically for 14 days in these studies. Complete heartburn relief in the first 24 hours was achieved by 39.5% of patients in the rabeprazole group in one of the studies and 31.3% of patients in the other study. Placebo response was 32.2 and 37.3%, respectively.

Acute efficacy with rabeprazole 10mg in heartburn varies, as expected, with the population studied and reflects experience with all PPIs. In a ‘pure’ ENRD population,
confirmed by endoscopy, efficacy with 10mg is at least as good as with higher doses, but a relatively high proportion of these sufferers may not achieve complete relief of their symptoms. This is because heartburn in ENRD is not always dependant on acid reflux and a proportion of this population will have causes for their symptoms not modifiable by acid suppression. Nonetheless PPIs represent the best available symptomatic treatment for this group as a whole.

Complete relief of heartburn symptoms was obtained in over 80% of patients with endoscopically confirmed ENRD or mild erosive GORD during 4 weeks of open label treatment to select patients in 2 studies examining the role of rabeprazole 10mg in ‘on demand’ maintenance of symptom control (see section below). This suggests that response to acute treatment may be dependant on population characteristics (e.g. frequency and severity of typical heartburn) other than endoscopic appearance. These findings also suggest that some patients may require longer acute treatment for complete remission of symptoms even if subsequent control can be maintained with shorter ‘bursts’ of drug.

Studies in uninvestigated heartburn populations treated with rabeprazole 10mg, reflect more closely the proposed ‘P’ population for Pariet Pharmacy. Again, experience with rabeprazole is in line with the general experience that PPIs provide complete relief in a higher proportion of this empirically treated population, comprising both patients with mild erosive and ENRD, than in patients with only ENRD. In the recent rabeprazole studies, heartburn sufferers were known to be responsive to some degree to acid-directed treatments (antacids and H2RAs) and therefore arguably more likely to respond to a PPI than a completely unselected population. In practice, many potential consumers of PPIs will have tried other acid control treatments with partial success.

Assessor’s comments:

The clinical study data provided by the applicant together with the clinical guideline recommendations of initial empirical treatment provides sufficient supporting evidence for the proposed OTC indication.

7. SAFETY

The MAH provided a safety summary which stated that phase II and III clinical studies (14 studies performed in North America and Europe in GU, DU and erosive GORD and 2 studies in GU and DU patients conducted in Japan) formed the basis for the original safety specification of rabeprazole. Subsequent clinical studies have examined efficacy in acute treatment of symptomatic GORD and, in Europe, in ‘on demand’ maintenance of symptom control.

The most commonly reported adverse drug reactions during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth.

As a result of post-marketing surveillance since launch, a number of uncommon, rare or very rare (frequency unknown) adverse events have been added to the product label by variation.
Rabeprazole is a well-tolerated drug with low incidence of adverse effects. The most frequently reported adverse events (e.g. headache, nausea and changes in bowel habit) tend to be mild and are often self-limiting. More serious adverse events are rare or very rare (e.g. blood dyscrasias, hepatic or renal effects, myalgia and arthralgia, hypersensitivity reactions and gynaecomastia) and tend to be idiosyncratic in nature and thus not predictable from baseline patient characteristics. Nonetheless warnings on the use of rabeprazole, e.g. in patients with a history of sensitivity to other substituted benzimidazoles derivatives and in patients with severe hepatic impairment, appear in the proposed label for Pariet Pharmacy.

Pariet Pharmacy is not intended for use in children and adolescents under 18 years and is contraindicated in pregnant and breast-feeding women. These limitations are common to all OTC PPI drugs for self-medication. However it is reassuring that experience with PPIs accumulated over 20 years of clinical use has not indicated particular safety concerns in pregnant women or children.

7.1 **Tolerability in Clinical Trials**

The MAH estimates that there have been over 98,123 patients exposed in clinical trials (interventional and non-interventional) since the International Birth Date. These studies do not suggest any significant change in the established safety profile of rabeprazole. That is, the adverse event profile seen in recent studies is comparable to what was seen during the initial marketing of rabeprazole.

7.2 **Post marketing surveillance**

Using the available wholesale data on the number of tablets sold and with the defined daily dose (DDD) for rabeprazole sodium (considered to be 10mg or 20mg), it is estimated that there have been over 11,410,556,248 patient-days of exposure from product launch through to 13 October 2010.

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**Assessor’s comments:**

*Since its marketing authorisation, rabeprazole has been used extensively and its safety profile is well characterised. The MAH provided a review of safety data of 10mg rabeprazole in the proposed pharmacy indication. Rabeprazole appears to be a well-tolerated drug with low incidence of adverse effects. Headache, nausea and changes in bowel habit are the most frequently reported adverse events and tend to be mild and are self-limiting. More serious adverse events (rare/very rare) such as blood dyscrasias, hepatic or renal effects, myalgia and arthralgia, hypersensitivity reactions and gynaecomastia are idiosyncratic in nature. Nonetheless warnings on the use of rabeprazole, e.g. in patients with a history of sensitivity to other substituted benzimidazoles derivatives and in patients with severe hepatic impairment, appear in the proposed label for Pariet Pharmacy.*

*In common with other OTC PPIs, Pariet Pharmacy is not intended for use in children under 18 years and is contraindicated in pregnant and breast-feeding women. It is reassuring that cumulative experience over 20 years of use has not indicated particular safety concerns in pregnant women or paediatric subgroups.*
8. ASSESSMENT OF POM CRITERIA

8.1 POM criterion 1

8.1.1 Direct danger to health

The total exposure to this drug is very large. See section 7.2 of this report.

The MAH states that in common with the entire class of proton pump inhibitors, rabeprazole is a well-tolerated drug with a low incidence of adverse effects. The most frequently reported adverse events (e.g. headache, nausea and changes in bowel habit) tend to be mild and often self-limiting. More serious adverse events are rare or very rare (e.g. blood dyscrasias, hepatic or renal effects, myalgia and arthralgia, hypersensitivity reactions and gynaecomastia) and tend to be idiosyncratic in nature and thus not predictable from baseline patient characteristics. Nonetheless suitable warnings on the use of rabeprazole e.g. in patients with a history of sensitivity to other substituted benzimidazoles derivatives and in patients with severe hepatic impairment, appear in the proposed label for Pariet Pharmacy.

Pariet Pharmacy is not intended for use in children under 18 years and is contraindicated in pregnant and breast-feeding women. These limitations are common to all acid-control drugs for self-medication.

Omeprazole 10mg is already approved as a ‘P’ category medicine for the symptomatic treatment of reflux symptoms. Initial dose is 20mg daily until symptoms are relieved. Subsequently, some patients may be able to control their symptoms with 10mg daily. Pantoprazole has been reclassified to a similar non-prescription status across all Member States (12 June 2009) for the short-term treatment of reflux symptoms. Thus two members of the PPI class have already been judged, against the prescription criteria, to be suitable for re-classification. Pariet Pharmacy is proposed as a pharmacy medicine for the same indications and has an adverse event profile which is not greatly different from omeprazole or pantoprazole and has many of the same adverse events listed (suggesting that at least some of these are class effects shared by substituted benzimidazoles). Rabeprazole, in contrast to omeprazole, has a notably low potential to produce interactions with drugs metabolised by the hepatic microsomal enzyme system (see below). In this respect rabeprazole can be considered to have at least as good an overall benefit-to-risk profile as similar drugs that already have ‘P’ status.

8.1.1.1 Drug Interactions

In rabeprazole’s metabolism a non-enzymatic pathway predominates. Metabolism by isoenzymes of the hepatic CYP450 system contributes a relatively small amount to the elimination of rabeprazole and the drug neither inhibits nor induces activity of this system. The propensity of rabeprazole to interact with other drugs handled by CYP450 is thus very limited. In contrast, PPI drugs heavily metabolised by this route (e.g. omeprazole) can inhibit the metabolism of a number of other medicines handled by the same system. This is the basis for potential interactions of omeprazole with e.g. diazepam, warfarin and phenytoin listed in the product label for ‘P’ omeprazole.
Assessor’s comments:

In vitro data show that rabeprazole thioether has an inhibition potential of CYP2C19 similar to omeprazole. However, the clinical relevance of this finding is unclear.

Although the successful reclassification of omeprazole and pantoprazole to OTC status does not set a precedent for this application. It is somewhat reassuring that there have been no significant changes to the risk: benefit profiles (from PSUR data) of these drugs as a result of their wider OTC availability. It is notable that there are fewer drug-drug interactions with rabeprazole compared with both pantoprazole and, in particular, omeprazole. Wider availability of a PPI with less potential for drug interaction could be of advantage to both pharmacist and patients, particularly as the sub-set of patients presenting with reflux-symptoms are often taking concomitant medication for other conditions.

All PPIs produce a profound inhibition of gastric acid secretion and therefore have the potential to reduce the plasma levels of drugs with absorption that is dependant on low pH. This is the basis for the Pariet Pharmacy label warning that levels of ketoconazole, itraconazole (oral anti-fungal agents) and atazanavir (a drug for HIV infection) may be sub-therapeutic if co-administered with rabeprazole.

Assessor’s comments:

The above drugs are listed in section 4.5 of the SPC and this is reflected in the patient information leaflet.

8.1.1.2 Adverse Events with PPIs - General Considerations Related to Long-term Use

Prolonged gastric hypo-acidity is associated with hypergastrinaemia which in turn can lead, in the long-term, to enterochromaffin-like (ECL) hyperplasia. Such hyperplasia might predispose to carcinoid tumour formation and has been speculated to potentially promote gastric carcinogenesis. PPI therapy may also alter the pattern and severity of H. Pylori-induced gastritis and accelerate gastric corpus gland loss, which in turn is thought to be a risk factor for gastric cancer. Despite these concerns, long term experience with PPIs has not been associated with an increased risk of gastric cancer.

All drugs that reduce gastric acidity increase bacterial counts of gut flora. These drugs may increase the risk of infections e.g. with Salmonella or Campylobacter, but whether PPIs might be a risk factor for Clostridium difficile-associated disease remains controversial.

Assessor’s comments:

As with other PPIs, section 4.4 of the SPC includes the following statement:

“Decreased gastric acidity, due to any means - including proton- pump inhibitors - increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid reducing drugs leads to a slightly increased risk of gastrointestinal
Other effects of sustained profound gastric hypoacidity, such as reduced calcium absorption contributing to risk of osteoporotic fractures or reduced B12 absorption, are possible with sustained long-term use of PPIs.

When used for symptomatic treatment of reflux, a condition characterised by relapses and remissions, continuous long-term use of PPIs is unlikely. People requiring continuous use to control symptoms are reminded by the Pariet Pharmacy PIL (see Annexe II) to consult their doctor. Through training materials, pharmacists are also alerted to the need for referral in these circumstances with all non-prescription drugs for heartburn and indigestion.

**Assessor’s comments:**

*The proposed short-term treatment duration is unlikely to cause sustained gastric hypoacidity.*

### 8.1.2 Indirect danger to health

The most important consideration relating to ‘indirect danger’ with all drugs used in the self-medication of acid-related gastrointestinal conditions is the potential for these drugs to mask the symptoms of gastric or oesophageal malignancy. In this regard it is important that potential consumers and pharmacists are reminded of symptoms and signs that increase the possibility of an underlying malignancy as the cause of presentation.

In the proposed SmPC for PARIET PHARMACY, under section 4.4 Warnings and Special Precautions for Use, the following section appears:

*Patients should be referred to their doctor if:*
  * They have had to take an indigestion or heartburn remedy continuously for 4 or more weeks in order to control their symptoms
  * They are aged over 55 years with new or recently changed symptoms
  * If they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, pain on swallowing, persistent vomiting or vomiting with blood, epigastric mass, previous gastric ulcer or surgery, jaundice or any other significant medical condition (including hepatic and renal impairment).

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 long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Patients aged over 55 years taking any “over the counter” (OTC, non-prescription) indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

This warning section is translated into easily understood language in the PIL as follows:

*Special advice for people taking medicines for indigestion or heartburn without a prescription*
You should talk to your pharmacist or doctor if:

- You need to take medicines for heartburn or indigestion for 4 weeks or more to control your symptoms.
- You are 55 years or older with symptoms that are new or recently changed. People in this age group should tell their pharmacist or doctor if they need to take treatment for their symptoms on a daily basis.
- You have lost weight without trying to: you have been told you are anaemic or you have had bleeding from your stomach or have black stools.
- You have difficulty swallowing or it is painful to swallow.
- You are being sick a lot or there is blood in your sick.
- You have noticed a lump in your stomach.
- You have had stomach ulcers in the past or surgery for ulcers.
- You have yellowing of the skin (jaundice) or any other serious illness.

You should not take other medicines to control stomach acid (e.g. other PPIs or tablets called H2 blockers) at the same time as this medicine.

This wording reflects both the current guidelines for the management of dyspepsia in General Practice, and the equivalent sections in all drug labels for non-prescription indigestion or heartburn remedies.

The British Society of Gastroenterology (BSG), NICE and NHS Clinical Knowledge Summary (CKS, formerly Prodigy Guidance) on dyspepsia have recommended 55 years as the age above which new symptoms or continuous symptoms should prompt further review and investigation. Gastro-oesophageal malignancy presents very rarely under the age of 55 years and so presentation below this age would not normally prompt endoscopy, unless other ‘alarm’ features were present from the list above.

Assessor’s comments:

The proposed SPC and PIL wording is acceptable.

8.1.3 Self-diagnosis

The classic symptom of rising retrosternal burning discomfort, often occurring after meals, is generally easily recognised and not often confused with e.g. cardiac pain that typically presents in relation to activity rather than food and is crushing in nature and frequently radiates to the left arm or neck.

In the UK there is a high prevalence (29%) of heartburn in the community. Population surveys in Western populations suggest that around 30% of sufferers have heartburn at least monthly, while 20% and 7% suffer weekly and daily respectively. Frequent and severe symptoms are more likely to prompt presentation but only 25% of all heartburn sufferers consult a doctor.

There is a poor correlation between severity of symptoms and endoscopic appearances and 70% of heartburn patients will have an apparently normal oesophageal mucosa. These endoscopy negative but symptomatic patients may have a range of causes for their heartburn including:
• High oesophageal acid exposure
• High sensitivity to oesophageal acid exposure
• Motility disorders and cross-over with functional dyspepsia

For this latter reason ENRD sufferers may have less than complete resolution of symptoms with a purely anti-secretory drug. Whether ENRD should be regarded as a completely different entity to erosive GORD is controversial, but there is general agreement that no or mild erosive changes have a benign course and seldom progress to severe erosive disease.

Patients with erosive changes generally have high levels of oesophageal acid exposure and respond well to PPIs. However healing of severe erosive changes and subsequent maintenance of symptom relief may require high doses for prolonged periods. Relapse of symptoms after healing is common in severe erosive GORD and symptoms are not well controlled with ‘on demand’ maintenance regimens.

Recognition and therefore ‘self-diagnosis’ of heartburn is straightforward. The great majority of heartburn sufferers have no or only mild erosive changes on endoscopy. For this reason, PPI treatment without investigation is advised for all those without warning symptoms indicating possible underlying malignancy. Thereafter, response to treatment governs further management. Satisfactory symptomatic control will be achieved in a high proportion of all heartburn sufferers with rabeprazole 10mg. Symptoms that respond poorly to PPIs or relapse readily unless continuous treatment is taken are readily identified and the product label for Pariet Pharmacy advises consultation with a pharmacist or doctor in such circumstances.

Assessor’s comments:

There are a wide range of OTC preparations available for GORD including other PPIs and H2RAs. The issue of diagnosing heartburn in the community pharmacy setting is already well established. There are no additional safety concerns relating to the use of rabeprazole to treat these symptoms.

Rabeprazole has a notably low propensity for drug interactions. The drug interactions that might occur would cause sub-therapeutic levels of drugs with acid-dependant absorption, rather than a risk of direct toxicity. Similarly, co-administration with another ‘acid suppressor’ (H2RAs) is unlikely to produce any serious unexpected adverse events.

Rabeprazole is very well tolerated even at doses greatly in excess of that proposed for Pariet Pharmacy; e.g. doses of 180mg daily have been used in Zollinger Ellison syndrome. Therefore the risk to health is small even if the dosage or recommended duration of treatment is exceeded. Since the maximum pack size of PARIENT PHARMACY will be 14 tablets of 10mg rabeprazole, even intentional overdose with the entire contents carries minimal risk as this amounts to just 140mg of rabeprazole per OTC pack.

The risk of masking serious underlying conditions as a result of ignoring dosage instructions for Pariet Pharmacy is no greater than with existing non-prescription drugs
for heartburn, including other PPIs. The label for Pariet Pharmacy contains appropriate warnings for consumers to mitigate this risk. Also pharmacists are well aware of this issue with all such drugs and will receive additional training material to emphasise the appropriate use of Pariet Pharmacy.

8.2 POM criterion 2

8.2.1 Safety related to abuse or misuse

Experience with other OTC PPI preparations containing omeprazole 10mg and pantoprazole 20mg for the same indications has not resulted in widespread incorrect use, and there is no reason to expect a different outcome with rabeprazole 10mg in the OTC environment when sold or supplied at a pharmacy under the supervision of a pharmacist.

**Risk of abuse**
Rabeprazole is not a controlled drug and has no documented psychotropic or narcotic pharmacology and therefore no addiction or illegal use is anticipated. There is no evidence for rabeprazole abuse and no evidence that it potentiates the effects of ethanol or drugs with abuse potential.

**Risk of misuse**
The proposed label for Pariet Pharmacy has relatively limited contraindications and special precautions for use. Use in contraindicated groups (e.g. children and pregnant women) is unlikely to be associated with serious adverse events on the basis of widespread experience of usage either inadvertently or on prescription in these groups.

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\begin{array}{|l|}
\hline
\text{Assessor’s comments:} \\
\text{The risks and consequences of overdose are minimal and the short-term treatment duration provides adequate safeguard against the risk of misuse. The risk of abuse or misuse is small.} \\
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\end{array}
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8.3 POM criterion 3

**Extensive Marketed Experience**
Rabeprazole has had wide usage as a prescription medicine. The first approval for marketing worldwide was in Japan on 14 October 1997 (International Birth date, IBD). The first date of approval in Europe for both the 10mg and 20mg tablet was in the UK 8 May 1998. Since those launches rabeprazole sodium has been approved for marketing in 99 countries.

Worldwide marketed use of rabeprazole (based on tablets sold with the defined daily dose for rabeprazole sodium considered to be 10mg or 20mg) is estimated to be over 11,410,556,248 patient-days of exposure from product launch through to 13 October 2010.

The MAH estimates that there have been over 98,123 patients exposed in clinical trials (interventional and non-interventional) since the International Birth Date (IBD).
Newly analysed studies do not suggest any significant change in the safety profile of rabeprazole. That is, the adverse event profile seen in recent studies is comparable to that seen during the initial marketing of rabeprazole.

**Strength, dose, route of administration, age group or indication**
The 10mg oral dose of rabeprazole sodium in Pariet Pharmacy is the lowest strength available on prescription. A daily dose of 10mg is used on prescription for a similar indication (symptomatic reflux without erosive oesophagitis) and for an identical initial dosage duration (maximum 4 weeks) as is proposed for Pariet Pharmacy.

A lower age limit of 18 years is proposed for self-medication usage, since use in children should be supervised by a physician.

Assessor’s comments:

*The MAH is currently undertaking clinical trials in the paediatric population as part of an approved Paediatric Investigational Plan. However, the proposed P product is not intended for paediatric use.*

*There are no safety concerns in relation to the third POM criterion.*

9. **PRODUCT INFORMATION**

9.1 **Summary of Product Characteristics**

The SPC has been extensively revised since the original application was submitted. The following amendments are outstanding at the time of writing:

The MAH proposed inclusion of the following information to section 5.1 of the SPC:

> ‘The percent of time the gastric pH remained above 3 following the administration of 10mg rabeprazole was similar to those after administration of 20mg tablet. Oral administration of 10mg or 20mg rabeprazole resulted in more than 4 or 5 fold decrease in intragastric acidity respectively, relative to placebo.’

The MAH provided supporting evidence for the proposed change with particular regard to the 10mg strength. In a randomised, double-blind placebo-controlled trial (Williams et al., 2000) with a cross-over design to compare the effects of 10mg, 20mg and 40 mg rabeprazole daily on intragastric acidity and plasma gastrin concentration, 24 healthy male volunteers had hourly intragastric acidity measurements taken via gastric aspiration for a 24-hour period on the 7th day of dosing. Plasma gastrin concentrations were also measured.

The percentage time for which intragastric pH was > 3 was 72%, 73% and 80% for rabeprazole 10, 20 and 40 mg, respectively. The corresponding values for pH > 4 were 59%, 63% and 71%.
The percentage of time the gastric pH remained above 3 following administration of rabeprazole was 72%. Similarly, the percentage of time the gastric pH remained above 3 following administration of 20 mg rabeprazole was 73%.

**Assessor’s comments:**

*Based on the evidence provided by Williams et al. the above paragraph should be amended as follows:*

*‘In a study involving 24 healthy volunteers following administration of 10 and 20mg rabeprazole for 7 days, the percent of time the gastric pH remained above 3 was 72% with 10mg and 73% with 20mg rabeprazole administration. In the same study oral administration of 10 or 20 mg rabeprazole resulted in an approximately 4 and 5-fold decrease in intragastric acidity (measured as 24-h median integrated acidity) respectively, relative to placebo.’*

### 9.2 Patient Information Leaflet

#### 9.2.1 User testing

The initial user testing report, was based on the POM product. Much of the report was not appropriate for the P product (e.g. many of the indications were not relevant) and many of the key safety messages were not tested. Therefore the MAH was requested to perform a separate, full user test for with ‘P’ leaflet.

The subsequent user test was specific to the reclassified product, particularly with respect to key safety messages and ability of subjects to adequately access important information from the leaflet. The results from the user test indicate that the proposed leaflet is legible, clear and easy to use and that potential patients will be able to locate, understand and appropriately act upon the information contained within the leaflet.

**Assessor’s comments:**

*The leaflet has undergone significant transformation and improvement since the original leaflet used in the abridge leaflet testing submission The amended leaflet complies with the requirements of Articles 59 (3) and 61(1) of Directive 2001/83EC, as amended, and the latest version is now considered acceptable and appropriate for a ‘P’ product.*

The applicant has confirmed that a Braille version of the final approved PIL will be made available to those individuals requesting this format.
9.3 Labelling

9.3.1 Carton
The carton in particular has undergone extensive revision since the original application. The print contrast, fonts and layout and general information are significantly improved from earlier versions. Minor text duplication errors on the mock-up have been removed and the carton is now approvable (Annex III).

9.3.2 Blister
The blister packs (derived from the prescription product) were originally calendared with the days of the week; suggestive of a course of medication; which was not appropriate. The days of the week have now been removed and the final blister artwork is appropriate.

9.3.3 Braille.
From the mock-up labels provided, the Braille position on the front of the carton is acceptable. Separate Braille labels have been submitted together with the appropriate translations.

In addition, the MAH confirms that a Braille patient information leaflet will be made available to those individuals requesting such a format.

10. PHARMACY PROTOCOL AND TRAINING

A document entitled Pariet Pharmacy Training Manual was provided as part of the submission. This contains the text that will be used in the final mock-up version of the pharmacy training material.

As this is the third PPI to be reclassified and given there are many other stomach medicines on the market, the main focus of the training material should be to enable the pharmacist to determine specifically when the product should be recommended and under what circumstances it is not appropriate to recommend Pariet Pharmacy. There is some general background information on GORD, but this is not the main focus of the training material, which centres around the use of the specific product and when to refer the patient, either to the pharmacist or to the patient’s physician, based on the cardinal warning signs for referral (age >55 years with new or recently changed symptoms, unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia etc.)

Assessor’s comments:

The training text provided is in line with proposed SPC information. The MAH is required to provide a mock-up of the training material for review, but its overall suitability as a training tool for pharmacists and pharmacy staff will be fully considered by the appropriate professional bodies. The MAH will be instructed to forward the final version materials to the professional bodies for discussion and, where necessary, amendment.
11. RISK MANAGEMENT PLAN

The MAH provided a corporate risk management plan for rabeprazole as part of its response to RFI, which did not include the risk management information for the proposed 10mg OTC product. As a result the MAH were asked to provide a revised RMP containing the missing information. As a result a completely revised RMP is being created which focuses on safe non-prescription supply of the 10mg rabeprazole product with pharmacist advice. The MAH was asked to emphasise the pharmacist being able to clearly distinguish between those conditions which can be treated and those that require referral to a physician. Discussions regarding the contents of the revised RMP have been had with the MAH.

Assessor’s comments:
The MAH was asked to provide an updated risk management plan, focusing on safe supply of the 10mg rabeprazole product with pharmacist advice. This has now been provided.

12. DISCUSSION

The proposed indications and safety warnings are in line with those PPIs already approved for OTC use. Pantoprazole and omeprazole are already available from the pharmacy without prescription.

The MAH was asked to provide an updated risk management plan, focusing on safe supply of the 10mg rabeprazole product with pharmacist advice. This has now been provided.

The pharmacy training and product labelling are important risk minimisation tools. The product labelling is appropriate for Pharmacy sale/supply. The final versions of the training materials for pharmacists and pharmacy support staff have yet to be provided as the MAH is updating these in line with previous RFI responses and discussions. Review of these training materials, together with full assessment of the RMP are the only significant outstanding requirements prior to conclusion of the reclassification procedure.

Efficacy data to support rabeprazole 10 mg for the reclassification from a prescription only medicine to a pharmacy only status medicine for the treatment of heartburn derives from study RAB-USA-2. In endoscopically negative subjects with moderately severe chronic GORD symptoms, both rabeprazole 10 mg and 20 mg once-daily doses showed significantly greater symptomatic relief than with placebo. Both doses were also significantly more effective than placebo for parameters such as time to first 48-hour and first daytime and night time heartburn-free intervals, percent of heartburn- and antacid-free periods, percentage of subjects with satisfactory relief, and virtually all average symptom scores and average daily consumption of antacids.

In common with the entire class of Proton Pump Inhibitors, rabeprazole is a well-tolerated drug with a low incidence of adverse effects. Clinical trials data from the MAH indicates that the most commonly reported adverse drug reactions were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The
majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

13. ADVICE SOUGHT

The Commission is asked to consider whether Pariet Pharmacy 10mg gastro-resistant tablets containing 10mg rabeprazole sodium falls within a description of class specified for the purpose of Section 58 of the Medicines Act 1968 by Order made under Section 58(1) as being appropriate for supply on a Prescription only basis in accordance with Section 58A(2) of that Act.

The proposed terms for P supply of Pariet Pharmacy are:

- tablets for oral administration
- short-term symptomatic treatment of gastro-oesophageal reflux-like symptoms
- adults aged 18 years and over
- maximum strength: 10mg rabeprazole sodium (equivalent to 9.42mg rabeprazole)
- maximum dose: 10mg
- maximum daily dose: 10mg
- maximum pack size: 14 tablets
Legal Classification

The Commission considered whether Pariet Pharmacy 10mg gastro-resistant tablets containing 10mg rabeprazole sodium falls within a description of class specified for the purpose of Section 58 of the Medicines Act 1968 by Order made under Section 58(1) as being appropriate for supply on a Prescription only basis in accordance with Section 58A(2) of that Act.

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- short-term symptomatic treatment of gastro-oesophageal reflux-like symptoms
- adults aged 18 years and over
- maximum strength: 10mg rabeprazole sodium (equivalent to 9.42mg rabeprazole)
- maximum dose: 10mg
- maximum daily dose: 10mg
- maximum pack size: 14 tablets

Marketing Authorisation

Approval of the reclassification is subject to the following amendments to Risk Management Plan and pharmacy training materials to the satisfaction of the Commission as follows:
1. Risk Management Plan
A fully revised Risk Management Plan should be made available for assessment, which includes specific reference to the proposed reclassified product.

2. Pharmacy protocol and training
Provision of the revised final educational material, based on the information contained in the final version product information (SmPC, labels and Patient Information Leaflet) for review.