Public Assessment Report

Decentralised Procedure

Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets

(rabeprazole sodium)

UK/H/1519/001-2/DC

UK licence no: PL 00289/1143-4

TEVA UK Limited
LAY SUMMARY

On the 1\textsuperscript{st} September 2010, the Medicine and Healthcare products Regulatory Agency (MHRA) granted TEVA UK Limited Marketing Authorisations (licences) for the medicinal products Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets (PL 00289/1143-4). These licences were granted via the decentralised procedure (UK/H/1519/001-2/DC), with the UK as the Reference Member State (RMS) and Austria, Belgium, Bulgaria, Denmark, Germany Greece, France, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Romania, Slovenia and Spain as Concerned Member States (CMS).

Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets contain the active ingredient rabeprazole sodium and works by reducing the production of acid in the stomach. This makes it possible for ulcers to heal, and thereby reduces pain. Rabeprazole Gastro-resistant Tablets are used to treat:

- Duodenal ulcers or benign gastric/stomach ulcers
- Gastro-oesophageal reflux disease associated with pain, discomfort and heartburn
- Zollinger-Ellison syndrome (patients with this condition contain extremely high amounts of acid in their stomachs)
- Peptic ulcer disease and given in combination with suitable antibiotics to remove the bacterium Helicobacter pylori

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

| **Product Name** | Rabeprazole Sodium 10 mg Gastro-resistant Tablets  
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<th>Rabeprazole Sodium 20 mg Gastro-resistant Tablets</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Rabeprazole sodium</td>
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<td><strong>Form</strong></td>
<td>Gastro-resistant tablets</td>
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</table>
| **Strength** | 10mg  
|              | 20mg                                              |
| **Marketing Authorisation Holder in the Reference Member State** | Teva UK Limited  
|              | Brampton Road, Hampden Park  
|              | Eastbourne, East Sussex, BN22 9AG, United Kingdom |
| **Reference Member State (RMS)** | UK                                                  |
| **Concerned Member State (CMS)** | Austria, Belgium, Bulgaria, Denmark, Germany Greece, France, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Romania, Slovenia and Spain. |
| **Procedure Number** | UK/H/1519/01-02/DC                                 |
| **End of Procedure** | 1\textsuperscript{st} September 2010              |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets (PL 00289/1143-4) is as follows. Differences are highlighted:

1 NAME OF THE MEDICINAL PRODUCT
Rabeprazole Sodium 10 mg Gastro-resistant Tablets
Rabeprazole Sodium 20 mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gastro-resistant tablet contains 10 mg of rabeprazole sodium.
Each gastro-resistant tablet contains 20 mg of rabeprazole sodium.

Excipients:
Each 10mg gastro-resistant tablet contains 0.34 mg of lactose.
Each 10mg gastro-resistant tablet contains 0.68 mg of lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.
Rabeprazole Sodium 10 mg Gastro-resistant Tablets: Pink, round tablet, imprinted on one side of the tablet with black ink "N" and "10".
Rabeprazole Sodium 20 mg Gastro-resistant Tablets: Yellow, round tablet, imprinted in black ink with "93" on one side and "64" on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Rabeprazole is indicated for the treatment of:
• Active duodenal ulcer
• Active benign gastric ulcer
• Symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD).
• Gastro-oesophageal reflux disease long-term management (GORD maintenance)
• Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD)
• Zollinger-Ellison syndrome
• In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori in patients with peptic ulcer disease (see section 4.2)

4.2 Posology and method of administration
Adults/elderly
Active duodenal ulcer and active benign gastric ulcer
The recommended oral dose for both active duodenal ulcer and active benign gastric ulcer is 20 mg to be taken once daily in the morning.

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

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

Erosive or ulcerative gastro-oesophageal reflux disease (GORD)
The recommended oral dose for this condition is 20 mg to be taken once daily for four to eight weeks.

Gastro-oesophageal reflux disease long-term management (GORD maintenance)
For long-term management, a maintenance dose of 10 mg or 20 mg once daily can be used depending upon patient response.

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

**Zollinger-Ellison syndrome**

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

**Eradication of H. pylori**

Patients with *H. pylori* infection should be treated with eradication therapy. The following combination given for 7 days is recommended.

Rabeprazole sodium 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily.

For indications requiring once daily treatment rabeprazole sodium should be taken in the morning, before eating; although neither the time of day nor food intake was shown to have any effect on its activity, this regimen will facilitate treatment compliance.

Patients should be cautioned that the 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 for use of rabeprazole sodium in the treatment of patients with severe hepatic impairment.

**Children**

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

4.3 **Contraindications**

Rabeprazole sodium is contra-indicated in patients with hypersensitivity to rabeprazole sodium or to any of the excipients.

Rabeprazole sodium is contra-indicated in pregnancy and during breast-feeding.

4.4 **Special warnings and precautions for use**

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 rabeprazole sodium.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

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

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

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

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

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 could not be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

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 rabeprazole sodium in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with rabeprazole sodium is first initiated in such patients.

Co-administration of atazanavir with rabeprazole sodium is not recommended (see section 4.5).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or
glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
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. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with rabeprazole sodium.

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

Co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH-dependent. Although not studied, similar results are expected with other proton pump inhibitors. Therefore PPIs, including 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 fetus due to rabeprazole sodium, although low feto-placental transfer occurs in rats. Rabeprazole sodium 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 rabeprazole sodium must 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 rabeprazole sodium 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 trials and post-marketing experience. Frequencies are defined as common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Infection</td>
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</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia</td>
<td>Leucopenia</td>
<td>Thrombocytopenia</td>
<td>Leucocytosis</td>
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<tr>
<td>Immune system disorders</td>
<td>Hyper sensitivity*</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Nervousness</td>
<td>Depression</td>
<td>Confusion</td>
<td></td>
</tr>
</tbody>
</table>
## Nervous system disorders
- Headache
- Dizziness
- Somnolence
- Visual disturbance

## Vascular disorders
- Peripheral oedema

## Respiratory, thoracic and mediastinal disorders
- Cough
- Pharyngitis
- Rhinitis
- Bronchitis
- Sinusitis

## Gastrointestinal disorders
- Diarrhoea
- Vomiting
- Nausea
- Abdominal pain
- Constipation
- Flatulence
- Dyspepsia
- Dry mouth
- Eruption

## Hepato-biliary disorders
- Hepatitis
- Jaundice
- Hepatic encephalopathy

## Skin and subcutaneous tissue disorders
- Rash
- Erythema
- Pruritis
- Sweating
- Bullous reactions
- Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)

## Musculoskeletal, connective tissue and bone disorders
- Non-specific pain
- Back pain
- Myalgia
- Leg cramps
- Arthralgia

## Renal and urinary disorders
- Urinary tract infection
- Interstitial nephritis

## Reproductive system and breast disorders
- Gynaecomastia

## General disorders and administration site conditions
- Asthenia
- Influenza like illness
- Chest pain
- Chills
- Pyrexia

## Investigations
- Increased hepatic enzymes
- Weight increased

* Includes facial swelling, hypotension and dyspnoea

** Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.

*** 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 rabeprazole sodium 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 60 mg twice daily, or 160 mg 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 antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H₂ histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (the acid or proton pump). The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

Anti-secretory activity
After oral administration of a 20 mg dose of rabeprazole sodium the onset of the anti-secretory effect occurs within one hour, with the maximum effect occurring within two to four hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole sodium are 69% and 82% respectively and the duration of inhibition lasts up to 48 hours. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Serum gastrin effects
In clinical studies patients were treated once daily with 10 or 20 mg rabeprazole sodium, for up to 43 months' duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion and remained stable while treatment was continued. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. Human gastric biopsy specimens from the antrum and the fundus from over 500 patients receiving rabeprazole or comparator treatment for up to 8 weeks have not detected changes in ECL cell histology, degree of gastritis, incidence of atrophic gastritis, intestinal metaplasia or distribution of H. pylori infection. In over 250 patients followed for 36 months of continuous therapy, no significant change in findings present at baseline was observed.

Other effects
Systemic effects of rabeprazole sodium in the CNS, cardiovascular and respiratory systems have not been found to date. Rabeprazole sodium, given in oral doses of 20 mg for 2 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathormone 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
Rabeprazole sodium is an enteric-coated (gastro-resistant) tablet formulation of rabeprazole sodium. This presentation is necessary because rabeprazole is acid-labile. Absorption of rabeprazole therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (Cmax) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma half-life is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. 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 *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 20 mg $^{14}$C-labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces.

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

Renal dysfunction
In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance \(\leq 5 \text{ ml/min/}1.73 \text{ m}^2\)), 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.

Hepatic dysfunction
Following a single 20 mg dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3 fold increase in half-life of rabeprazole compared to the healthy volunteers. However, following a 20 mg dose daily for 7 days the AUC had increased to only 1.5-fold and the \(C_{\text{max}}\) 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.

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

CYP2C19 polymorphism
Following a 20 mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and \(t_{\frac{1}{2}}\) 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 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 *in vivo* micronucleus and *in vivo* and *in vitro* DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Core:
Mannitol
Low-substituted hydroxypropylcellulose
Magnesium oxide, heavy
Hydroxypropylcellulose
Magnesium stearate
**Coating:**
- Hypromellose (E464)
- Cellulose, microcrystalline
- Stearic acid
- Titanium dioxide (E171)
- Hypromellose phthalate
- Triethyl citrate
- Lactose monohydrate
- Macrogol 4000
- Red iron oxide (E172)
- Yellow iron oxide (E172)

*In addition Black iron oxide (E172) - for Rabeprazole Sodium 20 mg Gastro-resistant Tablets only*

**Printing ink:**
- Shellac
- Black iron oxide (E172)
- N-butyl alcohol
- Purified water
- Industrial methylated spirit
- Propylene glycol
- 2-propanol
- Ethanol 96%

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
- Rabeprazole Sodium 10 mg Gastro-resistant Tablets: 18 months
- Rabeprazole Sodium 20 mg Gastro-resistant Tablets: 2 years

6.4 Special precautions for storage
- Store below 25°C.
- Store in original package in order to protect from moisture.

6.5 Nature and contents of container
- Aluminium/aluminium blister (PVC / aluminium / polyamide / aluminium) in outer carton containing 1, 7, 14, 15, 20, 25, 28, 30, 50, 56, 60, 75, 98, 100, and 120 gastro-resistant tablets.
- Hospital packs of 50 and 98 gastro-resistant tablets.
  *Not all pack sizes may be marketed.*

6.6 Special precautions for disposal
- No special requirements.

7 MARKETING AUTHORISATION HOLDER
- Teva UK Limited
  - Brampton Road,
  - Hampden Park,
  - Eastbourne,
  - East Sussex BN22 9AG
  - United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
- PL 00289/1143
- PL 00289/1144

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
- 06/10/2010

10 DATE OF REVISION OF THE TEXT
- 06/10/2010
Rabeprazole Sodium is not recommended at the same time as atazanavir as it could make atazanavir less effective.

- Ketocanazole oritraconazole, which are medicines used for treatment of fungal infections: your doctor may monitor you more closely and adjust the dose of ketoconazole oritraconazole if necessary.

- Pregnancy and breastfeeding:
  Do not use Rabeprazole Sodium if you are pregnant.
  - If you are breast-feeding (see ‘Do not take Rabeprazole Sodium’).
  
- Driving and using machines:
  It is very unlikely that Rabeprazole Sodium should impair the ability to drive or use machines. If you feel tired, you should avoid driving or using machines.

- Important information about some of the ingredients of Rabeprazole Sodium:
  This medicinal product contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

**HOW TO TAKE RABEPRAZOLE SODIUM**

**Dosage**

Always take Rabeprazole Sodium exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

- You should take Rabeprazole Sodium once daily, preferably before breakfast.
- The usual dose is 1 yellow (20 mg) or 1 pink (10 mg) gastro-resistant tablet daily.
- For duodenal ulcer or gastric ulcer (peptic ulcer), the doctor will prescribe 1 yellow (20 mg) tablet daily.
- For gastro-oesophageal reflux disease (GORD), the doctor will prescribe 1 yellow (20 mg) tablet daily.
- For GORD maintenance treatment, the doctor will prescribe 1 pink (10 mg) or 1 yellow (20 mg) tablet daily, depending on individual needs.
- For the treatment of moderate to severe Zollinger-Ellison syndrome, the doctor will prescribe 1 pink (10 mg) gastro-resistant tablet once daily.
- For the treatment of Zollinger-Ellison syndrome, the doctor will start by prescribing 3 yellow (20 mg) tablets a day, in one dose. Depending on how you respond to this dose, the doctor may then increase it up to 3 yellow (20 mg) tablets twice a day, if necessary.
- For the eradication of the Helicobacter pylori bacterium, the following treatment is recommended for 7 days: 1 yellow (20 mg) rabeprazole sodium gastro-resistant tablet twice daily, a clarithromycin 500 mg twice daily + amoxicillin 1 g twice daily.

**Method of administration**

The gastro-resistant tablet should be swallowed whole with sufficient liquid, preferably before breakfast. The tablet should not be chewed or crushed.

**Duration of treatment**

- If you have a duodenal ulcer: normally 4 weeks, but after this your doctor can decide to continue the treatment for 4 more weeks.
- If you have a stomach ulcer normally 6 weeks, but after this your doctor can decide to continue the treatment for 6 more weeks.
- If you have pain or discomfort due to reflux of stomach acid into the gut (GORD): 4-8 weeks.
- For GORD maintenance treatment, the doctor will decide for how long the tablets should be taken.
- If you are given symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease normally 4 weeks.
- For the eradication of the Helicobacter pylori bacterium, the normal treatment period is 7 days.
PAR Rabeprazole Sodium 10mg & 20mg Gastro-resistant Tablets UK/H/1519/01-2/DC

If you take more Rabeprazole Sodium than you should

Please contact your doctor if you have taken more Rabeprazole Sodium than you should.

If you forget to take Rabeprazole Sodium

If you have forgotten to take a dose, take it immediately when you remember, and continue the treatment as usual. If it is almost time to take the next dose, you should not take the forgotten tablet. Do not take a double dose to make up for a forgotten dose.

If you stop taking Rabeprazole Sodium

Normally, there will be relief of symptoms before the stomach ulcer is completely healed. It is therefore important that you do not stop taking the gastro-resistant tablets before your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Rabeprazole Sodium can cause side effects, although not everybody gets them.

If any of these symptoms appear, you should stop treatment with Rabeprazole Sodium and contact your doctor.

- Hypersensitivity reactions which may appear as a skin rash, redness of the skin, itching and rarely side blisters, liver problems and acute generalized reactions for example: facial swelling, low blood pressure and shortness of breath, all of which should resolve after stopping the treatment. This is a rare side effect (affect 1 to 10 users in 10,000).
- Unexplained bruising, or fever and serious deterioration of your general condition or local infection symptoms such as a persistent sore throat, mouth ulcers or urinary problems, which may indicate a change in the number of your blood cells (see "Take special care with Rabeprazole Sodium", above). This is a rare side effect (affect 1 to 10 users in 10,000).
- Hepatitis inflammation of the liver which may make you feel tired, with yellowing of the eyes or skin, dark urine, jaundice (yellowing of the skin and whites of the eyes). These are rare side effects (affect 1 to 10 users in 10,000), which sometimes may lead to liver disease.
- Serious skin reactions with red, irregular rash, blisters and/or skin loss. These are very rare side effects (affect less than 1 user in 10,000).

The following side effects have also been reported:

Common side effects (affect 1 to 10 users in 100):
- Incontinence, headache, dizziness.
- Cough, sore throat, runny nose.
- Diarrhoea, feeling or being sick, abdominal pain, constipation, wind.
- Pain including back pain.
- Infection.
- Tiredness, "flu-like" illness.

Uncommon side effects (affect 1 to 10 users in 1,000):
- Nervousness, sleeplessness.
- Bronchitis, sinusitis.
- Indigestion, dry mouth, belching.
- Rash, reddening of the skin.
- Muscle pain, leg cramps, joint pain.
- Urinary tract infection.
- Chest pain, change in color, fever.
- Abnormal liver function test results.

Rare side effects (affect 1 to 10 users in 10,000):
- Visual disturbance.
- Inflammation of the stomach or mouth, taste disturbance.
- Kidney disease.
- Itching, sweating, blistering.
- Loss of appetite.
- Weight gain.
- Depressions.

Other side effects, the frequency of which is unknown:
- Confusion.
- Low blood sodium levels.
- Swelling in the limbs.
- Breast tenderness.

The doctor should always be contacted if side effects result in unacceptable discomfort.

For further information on the patient information leaflet, ask your pharmacist or see the individual product information leaflet.

5. HOW TO STORE RABEPRAZOLE SODIUM

Keep out of the reach and sight of children.

Store below 25°C.

Store in original package in order to protect from moisture.

Do not use Rabeprazole Sodium after the expiry date which is stated on the pack. 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 no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Rabeprazole Sodium contains

The active substance is rabeprazole sodium.

- Each 10 mg gastro-resistant tablet contains 10 mg rabeprazole sodium.
- Each 20 mg gastro-resistant tablet contains 20 mg rabeprazole sodium.

The other ingredients are:
- Core: Mannitol, low substituted hydroxypropylcellulose, magnesium oxide, hygroscopic hydrogenated stearic acid, magnesium stearate.

Coating - 10 mg tablets:
- Hypromellose (E464), cellulose, microcrystalline, stearic acid, titanium dioxide (E171), hypromellose phtalate, triethyl citrate, lactose monohydrate, microcrystalline, red iron oxide (E172), yellow iron oxide (E172).

Coating - 20 mg tablets:
- Hypromellose (E464), cellulose, microcrystalline, stearic acid, titanium dioxide (E171), hypromellose phtalate, triethyl citrate, lactose monohydrate, microcrystalline, red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172).

Printing ink:
- Shellac, black iron oxide (E172). propylene glycol, ethylalcohol, 2-propanol, purified water, industrial methylated spirit, ethanol 96%.

What Rabeprazole Sodium looks like and contents of the pack

- Rabeprazole Sodium 10mg Gastro resistant Tablets are pink, round tablets, imprinted on one side of the tablet with black ink "10" and "10".
- Rabeprazole Sodium 20mg Gastro resistant Tablets are yellow, round tablets, imprinted in black ink with "20" on each side and "20" on the other.

Rabeprazole sodium gastro-resistant tablets are available in pack sizes of 1, 7, 14, 15, 20, 25, 30, 60, 90, 60, 76, 89, 100 and 120 gastro-resistant tablets. Hospital packs of 50 and 98 gastro-resistant tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
TEVA UK Limited, Eastbourne BN22 9AG.

This leaflet was last revised in October 2010.

PL 002/89/143-1144
Module 4
Labelling

Carton
I  INTRODUCTION
On 1st September 2010, Austria, Belgium, Bulgaria, Denmark, Germany, Greece, France, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Romania, Slovenia, Spain and the UK agreed to grant Marketing Authorisations (MAs) to TEVA UK Limited for the medicinal products Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets. The MAs were granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/1519/01-02/DC). After the national phase, MAs were granted in the UK on 6th October 2010 (PL 00289/1143-44). These products are a prescription-only medicines.

These applications were made under Article 10.1 of Directive 2001/83/EC for Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets, containing the known active substance rabeprazole sodium. The reference medicinal products for this application are Pariet® 10mg and 20mg (PL 10555/0010 and PL 10555/0008 respectively), both licensed on the 8th May 1998 to Eisai Limited. The reference products have been authorised in the EEA for more than 10 years, so the period of data exclusivity has expired.

Rabeprazole belongs to the substituted benzimidazole class of anti-secretory compounds that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme (the acid or proton pump). Proton Pump Inhibitors (PPIs) reduce stomach acid by blocking the enzyme system responsible for active transport of acid into the gastrointestinal lumen of the gastric parietal cell, also known as the ‘proton pump’. Inactivation of proton pumps is accomplished by covalent binding of sulphenamides to the proton pumps’ cysteine residues.

No new preclinical or clinical studies were conducted for these applications, which is acceptable given that the applications are for generic versions of products that have been licensed for over 10 years. Two bioequivalence studies have been provided to support these applications.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH 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. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk
minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active substance is well established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This is an application for a generic product and there is no reason to conclude that the marketing of this product will change the overall use pattern of the existing market.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State (RMS) | Rabeprazole Sodium 10 mg Gastro-resistant Tablets  
Rabeprazole Sodium 20 mg Gastro-resistant Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Rabeprazole sodium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>A02B C04</td>
</tr>
</tbody>
</table>
| Pharmaceutical form and strength(s)                  | Gastro-resistant tablets  
10 and 20mg                                                                 |
| Reference numbers for the Decentralised Procedure     | UK/H/1519/01-02/DC                                                                               |
| Reference Member State                                | United Kingdom                                                                                   |
| Member States concerned                               | Austria, Belgium, Bulgaria, Denmark, Germany, Greece, France, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Romania, Slovenia and Spain. |
| Marketing Authorisation Number(s)                     | PL 00289/1143-4                                                                                  |
| Name and address of the authorisation holder in the RMS| Teva UK Limited  
Brampton Road, Hampden Park  
Eastbourne, East Sussex, BN22 9AG, United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN Rabeprazole sodium
Chemical name: 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1H-benzimidazole sodium

Structure:

Empirical formula: 
C_{18}H_{20}N_{3}O_{3}SNa

Molecular weight: 381.43

General Properties
Description: White to yellowish white crystalline powder

Solubility: Soluble in water.

The active substance, rabeprazole sodium, is not the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Manufacture
Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

The active substance is stored in appropriate packaging. The substance is packaged in clear low density polyethylene (LDPE) bags. Each bag is placed inside a black LDPE bag with silica gel and heat sealed. The double polyethylene bag pack is placed in a triple laminated bag, sealed and kept inside a high density polyethylene (HDPE) container. It is stated that the immediate LDPE container complies with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs and pharmaceuticals. Specifications and Certificates of Analysis have been provided for the packaging materials used.

Appropriate stability data have been generated by the active substance manufacturer for
active substance stored in the proposed commercial packaging. Based on the data, a retest period of 24 months has been set, when the active is stored in the proposed packaging.

**DRUG PRODUCT**

**Description and Composition**

Rabeprazole Sodium 10mg Gastro-resistant Tablets are presented as pink, round tablet, imprinted on one side of the tablet with black ink "N" and "10". Each tablet contains 10mg of the active ingredient, rabeprazole sodium.

Rabeprazole Sodium 20mg Gastro-resistant Tablets are presented as Yellow, round tablet, imprinted in black ink with "93" on one side and "64" on the other. Each tablet contains 20mg of the active ingredient, rabeprazole sodium.

Other ingredients consist of pharmaceutical excipients, namely mannitol, low-substituted hydroxypropylcellulose, magnesium oxide, heavy, hydroxypropylcellulose and magnesium stearate making up the tablet core; hypromellose (E464),cellulose, microcrystalline, stearic acid, titanium dioxide (E171), hypromellose phthalate, triethyl citrate, lactose monohydrate, macrogol 4000, red iron oxide (E172), yellow iron oxide (E172) and (Black iron oxide (E172)- 20mg strength only) making up the tablet coating; and shellac, black iron oxide (E172), N-butyl alcohol, purified water, industrial methylated spirit, propylene glycol, 2-propanol and ethanol 96% making up the printing ink. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopeia monographs, with the exception of the iron oxides (black, red and yellow) which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

**Pharmaceutical Development**

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The aim was to develop medicinal products bioequivalent and pharmaceutically equivalent to the reference products, Pariet® 10mg and 20mg (PL 10555/0010 and PL 10555/0008 respectively, Eisai Limited).

**Dissolution and Impurity Profiles**

Dissolution and impurity data were provided for the proposed products and were found to be satisfactory.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. All validation data were within specification.

**Finished Product Specification**

Finished product specifications are provided for both release and shelf–life, and are
satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Batch data are provided for all strengths of the finished product, which demonstrate that the batches are compliant with the proposed release specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**
The finished product is licensed for marketing in aluminium/aluminium blister strips (comprising of polyvinylchloride/aluminium/polyamide), which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 1, 7, 14, 15, 20, 25, 28, 30, 50, 50, 56, 57, 60, 75, 98, 100 and 120 tablets and hospitals packs of 50 and 98 tablets. The MAH has stated that not all pack sizes may be marketed and has committed to submit mock-ups for all packaging for assessment before those pack sizes are commercially marketed. All primary product packaging complies with Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 18 months and 2 years has been set for Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets respectively, which is satisfactory. Storage conditions are “Do not store above 25°C” and “Store in the original package in order to protect from moisture”.

**Bioequivalence Study**
Two bioequivalence studies were presented (fed and fasting conditions) comparing the test product, Rabeprazole Sodium 20mg Gastro-resistant Tablet, to the reference product, Pariet® 20mg Tablets (MA Holder: Eisai Ltd., UK).

An evaluation of the bioequivalence studies is found in the Clinical Aspects section.

**Quality Overall Summary**
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL 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 the leaflet contains.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Conclusion**
The test product corresponds to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative...
composition in terms of the active substance and pharmaceutical form. On this basis and considering the bioequivalence data provided, the applicant’s claim that Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets are generic medicinal products of Pariet® 10mg and 20mg Tablets – PL 10555/0010 and PL 10555/0008 (MA Holder: Eisai Ltd., UK), is justified.

There are no objections to approval of Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of rabeprazole sodium are well-known. Therefore, no further studies are required and the applicant has provided none.

The pre-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

The SmPC is satisfactory from a pre-clinical viewpoint.

There are no objections to approval of Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets from a pre-clinical point of view.

III.3 CLINICAL ASPECTS

Clinical aspects

The application is supported by two bioequivalence studies presented by the applicant, comparing the pharmacokinetic profiles of Rabeprazole Sodium 20mg Gastro-resistant (test) and Pariet® 20mg gastro-resistant tablets, Eisai Limited, UK (PL 10555/0008) under fed and fasting conditions.

The studies were of an appropriate design and were conducted in accordance with the principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference products. The use of the 20mg strength only for the bioequivalence studies has been adequately justified.

*Pharmacokinetics*

**Fasting Study**

This was a randomised, single dose, open label, two treatments, four period, two sequence, replicate crossover bioavailability study conducted in fifty healthy individuals under fasting conditions. Each subject received both treatments in accordance with a randomization code; single oral doses of each formulation were given under fasting conditions. Following an overnight fast of 10 hours, a single dose of the investigational products were administered orally, with water, to each subject in each period. A washout period of at least seven days separated the two dosing days.

**Analytical methods:**

Blood samples were taken pre-dose and at specified time points up to 14 hours after administration of test or reference product. Samples were analysed for rabeprazole sodium using a validated analytical method using a validated High Performance Liquid Chromatography coupled with tandem Mass Spectrometry methodology.
The primary pharmacokinetic variables for determining bioequivalence were \( C_{\text{max}} \), \( \text{AUC}_t \) and \( \text{AUC}_\infty \).

**Statistical methods**  
Analysis of variance (ANOVA) would be performed on natural log-transformed pharmacokinetic parameters \( C_{\text{max}} \), \( \text{AUC}_\infty \) and \( \text{AUC} \).

**Results:**  
50 subjects were enrolled in the study, 48 subjects were included in the pharmacokinetic and statistical analyses. 45 subjects completed the study. None of the protocol deviations appear to have had a significant impact on the safety or integrity of the study results.

The summary of the results of the bioequivalence study are tabulated below.

**Summary of Pharmacokinetic Parameters for Rabeprazole 20mg – geometric mean (n=47)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_t )</th>
<th>( \text{AUC}_\infty )</th>
<th>( C_{\text{max}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>696.18</td>
<td>705.66</td>
<td>437.28</td>
</tr>
<tr>
<td>Reference</td>
<td>743.54</td>
<td>753.69</td>
<td>478.03</td>
</tr>
</tbody>
</table>

ANOVA 90% CI (Log transformed) and CV% for primary parameters of Rabeprazole (test vs. reference).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geometric mean</th>
<th>Confidence limits</th>
<th>Intra-individual CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_t ) (ratio test/reference)</td>
<td>93.63</td>
<td>88.89 – 98.63</td>
<td>20.2 (A) 18.9 (B)</td>
</tr>
<tr>
<td>( \text{AUC}_\infty ) (ratio test/reference)</td>
<td>93.63</td>
<td>89.09 – 98.40</td>
<td>19.3 (A) 17.5 (B)</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ratio test/reference)</td>
<td>91.48</td>
<td>83.84 – 99.81</td>
<td>42.3 (A) 29.4 (B)</td>
</tr>
</tbody>
</table>

**Conclusion on bioequivalence study:**  
The results of the bioequivalence study show that the 20mg strength test and reference products are bioequivalent under fasting conditions, as confidence intervals for \( \text{AUC}_t \), \( \text{AUC}_\infty \) and \( C_{\text{max}} \) fall within the acceptance criteria ranges of 80.00 and 125.00% in-line with current guidelines.

No serious adverse events were recorded in this study. The safety results were comparable between products.

**Fed State Study**  
This was a randomised, single dose, open label, two treatments, four period, two sequence, replicate crossover bioavailability study conducted in fifty healthy individuals under fed conditions. A single dose of the investigational products were administered orally, with water, to each subject in each period 30 minutes after eating a standardised high fat, high calorie breakfast. Each subject received both treatments in accordance with a randomization code; single oral doses of each formulation were given under fed conditions. A washout period of at least seven days separated the two dosing days.

**Analytical methods**  
Blood samples were taken pre-dose and at specified time points up to 36 hours after administration of test or reference product.
Samples were analysed for rabeprazole sodium using a validated analytical method using a validated High Performance Liquid Chromatography coupled with tandem Mass Spectrometry methodology.

The primary pharmacokinetic variables for determining bioequivalence were C<sub>max</sub>, AUC<sub>t</sub> and AUC<sub>∞</sub>.

**Statistical methods**

Analysis of variance (ANOVA) would be performed on natural log-transformed pharmacokinetic parameters C<sub>max</sub>, AUC<sub>∞</sub> and AUC.<

**Results**

50 subjects were enrolled in the study, 48 subjects were included in the pharmacokinetic and statistical analyses. 45 subjects completed the study. None of the protocol deviations appear to have had a significant impact on the safety or integrity of the study results.

The summary of the results of the bioequivalence study are tabulated below.

**Summary of Pharmacokinetic Parameters for Rabeprazole 20mg –geometric mean (n=48)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;t&lt;/sub&gt; ng/ml/h</th>
<th>AUC&lt;sub&gt;∞&lt;/sub&gt; ng/ml</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>474.33</td>
<td>477.17</td>
<td>261.47</td>
</tr>
<tr>
<td>Reference</td>
<td>464.72</td>
<td>474.54</td>
<td>246.07</td>
</tr>
</tbody>
</table>

ANOVA 90% CI (Log transformed) and CV% for primary parameters of Rabeprazole (test vs. reference).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geometric mean</th>
<th>Confidence limits</th>
<th>Intra-individual CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;t&lt;/sub&gt;</td>
<td>102.07</td>
<td>93.89 – 110.96</td>
<td>36.1 (A) 34.1 (B)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt;</td>
<td>100.55</td>
<td>92.72 – 109.05</td>
<td>34.5 (A) 31.5 (B)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>106.26</td>
<td>92.01 – 122.72</td>
<td>57.9 (A) 68.4 (B)</td>
</tr>
</tbody>
</table>

**Conclusion on bioequivalence study:**

The results of the bioequivalence study show that the 20mg strength test and reference products are bioequivalent under fed conditions, as confidence intervals for AUC<sub>t</sub>, AUC<sub>∞</sub> and C<sub>max</sub> fall within the acceptance criteria ranges of 80.00 and 125.00% in-line with current guidelines.

No serious adverse events were recorded in this study. The safety results were comparable between products.

**Pharmacokinetic conclusion**

Bioequivalence studies submitted for Rabeprazole sodium 20mg Gastro-resistant Tablets, show that the test and the reference product are bioequivalent under fed and fasting states, as the conventional bioequivalence intervals for C<sub>max</sub>, AUC<sub>t</sub> and AUC<sub>∞</sub> fall within the acceptance criteria of 80 – 125% in-line with the current guidelines.

Satisfactory justification is provided for a bio-waiver for Rabeprazole Sodium 10mg Gastro-
resistant Tablets. As Rabeprazole Sodium 10mg Gastro-resistant Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev1/Corr), the results and conclusions of the bioequivalence study on the 20mg strength can be extrapolated to the 10mg strength tablets.

**Pharmacodynamic studies**
No new data submitted or required.

**Clinical efficacy**
No new data have been submitted and none are required. The reference product is established and the application depends upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of rabeprazole sodium is well-established from its extensive use in clinical practice.

**Clinical safety**
No new data have been submitted and none are required for application of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of rabeprazole sodium is well-known.

**Benefit-Risk assessment**

Rabeprazole sodium, when used as indicated, has a favourable benefit-to-risk profile. As shown in the various clinical settings patients have drawn benefit from therapy with rabeprazole sodium.

Bioequivalence has been demonstrated. The formulation of Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets can be considered essentially similar to innovator products Pariet® 10mg and 20mg. The efficacy and safety profiles of the two products would therefore be expected to be equivalent.

**PRODUCT INFORMATION:**
**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC and PIL are clinically acceptable, and consistent with those for the reference product. The labelling is clinically acceptable and in-line with current requirements.

**Expert Report**
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

**Conclusion**
The bioequivalence studies were of appropriate design and demonstrate the bioequivalence of the test (Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets) and reference (Pariet® 10mg and 20mg Tablets, Eisai Limited-PL 10555/0010 and PL 10555/0008 respectively) products within the agreed acceptance limits under fed and fasting states.

Sufficient clinical information has been submitted to support this application. When used as indicated, the product has a favourable benefit-to-risk ratio. A Marketing Authorisation was therefore granted.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new pre-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets, and the reference products, Pariet® 10mg and 20mg Tablets, (Eisai Limited) under fed and fasting states.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC and PIL are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears in the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Rabeprazole Sodium 10mg and 20mg Gastro-resistant Tablets and the reference products Pariet® 10mg and 20mg Tablets, (Eisai Limited-PL 10555/0010 and PL 10555/0008 respectively) are interchangeable. Extensive clinical experience with rabeprazole sodium is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk ratio is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 July 2012</td>
<td>Medical Variation Type 1B</td>
<td>To delete, the therapeutic indication, for eradication of Helicobacter pylori in patients with peptic ulcer disease. As a consequence, Sections 4.1 (Therapeutic indications) and 4.2 (Posology and method of administration) of the Summary of Product Characteristics (SmPC) and the leaflet have been updated.</td>
<td>Approved</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 00289/1143-0019
PL 00289/1144-0020

Product: Rabeprazole Sodium 10mg Gastro-resistant Tablets
Rabeprazole Sodium 20mg Gastro-resistant Tablets

Marketing Authorisation Holder: Teva UK Limited

Active Ingredient(s): Rabeprazole sodium

Reason:
To delete, the therapeutic indication, for eradication of Helicobacter pylori in patients with peptic ulcer disease. As a consequence, Sections 4.1 (Therapeutic indications) and 4.2 (Posology and method of administration) of the Summary of Product Characteristics (SmPC) and the leaflet have been updated.

Supporting Evidence
Revised SmPC and leaflet have been provided.

Evaluation
The final SmPC fragments and the leaflet are acceptable.

The final granted SmPC fragments are presented below:

SUMMARY OF PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Rabeprazole is indicated for the treatment of:
- Active duodenal ulcer
- Active benign gastric ulcer
- Symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD).
- Gastro-oesophageal reflux disease long-term management (GORD maintenance)
- Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD)
- Zollinger-Ellison syndrome

4.2 Posology and method of administration
Adults/elderly
Active duodenal ulcer and active benign gastric ulcer
The recommended oral dose for both active duodenal ulcer and active benign gastric ulcer is 20 mg to be taken once daily in the morning.

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

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

Erosive or ulcerative gastro-oesophageal reflux disease (GORD)
The recommended oral dose for this condition is 20 mg to be taken once daily for four to eight weeks.

_Gastro-oesophageal reflux disease long-term management (GORD maintenance)_
For long-term management, a maintenance dose of 10 mg or 20 mg once daily can be used depending upon patient response.

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

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

For indications requiring once daily treatment rabeprazole sodium should be taken in the morning, before eating; although neither the time of day nor food intake was shown to have any effect on its activity, this regimen will facilitate treatment compliance.

Patients should be cautioned that the 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 for use of rabeprazole sodium in the treatment of patients with severe hepatic impairment.

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

The final granted leaflet is published on the MHRA website.

**Conclusion**
The proposed SmPC and the leaflet amendments are in-line with the reference product and there are no objections to approval.

**Decision**
Approved (05 September 2012/19 September 2012)