

Public Assessment Report

Scientific discussion

**Rabeprazolnatrium 10 mg and 20 mg Teva,
gastro-resistant tablets
(rabeprazole sodium)**

NL/H/4542/001-002/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Rabeprazolnatrium 10 mg and 20 mg Teva, gastro-resistant tablets. The procedure was finalised in the United Kingdom (UK/H/1519/001-002/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

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 1st 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	Rabepazole Sodium 10 mg Gastro-resistant Tablets Rabepazole Sodium 20 mg Gastro-resistant Tablets
Type of Application	Generic, Article 10.1
Active Substance	Rabepazole sodium
Form	Gastro-resistant tablets
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 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 fetoplacental 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 ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System organ class	Common	Uncommon	Rare	Very rare	Not known
<i>Infections and infestations</i>	Infection				
<i>Blood and the lymphatic system disorders</i>			Neutropenia Leucopenia Thrombocytopenia Leucocytosis		
<i>Immune system disorders</i>			Hypersensitivity*, **		
<i>Metabolism and nutrition disorders</i>			Anorexia		Hyponatremia
<i>Psychiatric disorders</i>	Insomnia	Nervousness	Depression		Confusion

<i>Nervous system disorders</i>	Headache Dizziness	Somnolence			
<i>Eye disorders</i>			Visual disturbance		
<i>Vascular disorders</i>					Peripheral oedema
<i>Respiratory, thoracic and mediastinal disorders</i>	Cough Pharyngitis Rhinitis	Bronchitis Sinusitis			
<i>Gastrointestinal disorders</i>	Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance		
<i>Hepato-biliary disorders</i>			Hepatitis Jaundice Hepatic encephalopathy ***		
<i>Skin and subcutaneous tissue disorders</i>		Rash Erythema**	Pruritis Sweating Bullous reactions**	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	
<i>Musculoskeletal, connective tissue and bone disorders</i>	Non-specific pain Back pain	Myalgia Leg cramps Arthralgia			
<i>Renal and urinary disorders</i>		Urinary tract infection	Interstitial nephritis		
<i>Reproductive system and breast disorders</i>					Gynaecomastia
<i>General disorders and administration site conditions</i>	Asthenia Influenza like illness	Chest pain Chills Pyrexia			
<i>Investigations</i>		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 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

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 (C_{max}) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma half-life is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. 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 ¹⁴C-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 ≤ 5 ml/min/1.73 m²), the disposition of rabeprazole was very similar to that in healthy volunteers. The AUC and the C_{max} in these patients was about 35% lower than the corresponding parameters in healthy volunteers. The mean half-life of rabeprazole was 0.82 hours in healthy volunteers, 0.95 hours in patients during haemodialysis and 3.6 hours post-dialysis. The clearance of the drug in patients with renal disease requiring maintenance haemodialysis was approximately twice that in healthy volunteers.

Hepatic dysfunction

Following a single 20 mg dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3 fold increase in half-life of rabeprazole compared to the healthy volunteers. However, following a 20 mg dose daily for 7 days the AUC had increased to only 1.5-fold and the C_{max} to only 1.2-fold. The half-life of rabeprazole in patients with hepatic impairment was 12.3 hours compared to 2.1 hours in healthy volunteers. The pharmacodynamic response (gastric pH control) in the two groups was clinically comparable.

Elderly

Elimination of rabeprazole was somewhat decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled, the C_{max} increased by 60% and t_{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_{1/2} which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolisers whilst C_{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 : 2years

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, 57, 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

Module 2

PATIENT INFORMATION LEAFLET

RABEPRAZOLE SODIUM 10 & 20 mg GASTRO-RESISTANT TABLETS

PACKAGE LEAFLET INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1. What Rabeprazole Sodium is and what it is used for
2. Before you take Rabeprazole Sodium
3. How to take Rabeprazole Sodium
4. Possible side effects
5. How to store Rabeprazole Sodium
6. Further information

1 WHAT RABEPRAZOLE SODIUM IS AND WHAT IT IS USED FOR

Rabeprazole belongs to a group of drugs called proton pump inhibitors, which work by reducing the production of acid in the stomach. This makes it possible for ulcers to heal, and thereby reduces pain.

Rabeprazole Sodium Gastro-resistant Tablets are used:

- To treat duodenal ulcers or benign gastric/stomach ulcers (peptic ulcers)
- To treat gastro-oesophageal reflux disease (GORD), commonly referred to as inflammation of the gullet, associated with pain, discomfort and heartburn caused by reflux of stomach acid into the gullet, including moderate to very severe versions of the disease
- For the long-term treatment of GORD, to prevent recurrence of the disease after the symptoms have disappeared (GORD maintenance)
- In patients whose stomachs may contain extremely high amounts of acid, a condition called Zollinger-Ellison syndrome
- In combination with suitable antibiotics, to remove the bacterium *Helicobacter pylori* (*H. pylori*) in patients with peptic ulcer disease.

2 BEFORE YOU TAKE RABEPRAZOLE SODIUM

Do not take Rabeprazole Sodium

- if you are **allergic** (hypersensitive) to **rabeprazole sodium** or any of the other ingredients of Rabeprazole Sodium
- if you are **pregnant** or **breast-feeding**.

Take special care with Rabeprazole Sodium

- If you are allergic to other proton pump inhibitors belonging to the benzimidazole group (e.g. omeprazole or pantoprazole), you may also be allergic to rabeprazole
- Consult your doctor if you have **liver disease**: he/she may need to prescribe a different dose for you
- **Rabeprazole Sodium is not recommended for use in children**
- Treatment with rabeprazole sodium is not recommended at the same time as taking atazanavir (used for HIV/AIDS) (see 'Taking other medicines' below)
- There have been reports of patients developing reduced levels of blood platelets or white blood cells during treatment with rabeprazole sodium, which mostly returned to normal after the end of treatment. If you notice unexplained bruising during your treatment with rabeprazole sodium, you should contact your doctor.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Rabeprazole Sodium can influence the effect of some other medicines e.g.:

- Atazanavir, which is used for HIV/AIDS:

Rabeprazole Sodium is not recommended at the same time as atazanavir as it could make atazanavir less effective

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

Pregnancy and breast-feeding

Do not use Rabeprazole Sodium if you are pregnant, think you are pregnant or if you are breast-feeding (see 'Do not take Rabeprazole Sodium').

Ask your doctor or pharmacist for advice before taking any medicine.

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 an intolerance to some sugars, contact your doctor before taking this medicinal product.

3 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 not sure.

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** and **benign gastric 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 symptomatic treatment of **moderate to very serious GORD**, 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 + clarithromycin 500 mg twice daily + amoxicillin 1 g twice daily.

Method of administration

The gastro-resistant tablet should be swallowed whole with sufficient liquid, preferable 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 gullet (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 serious gastro-oesophageal reflux disease: normally 4 weeks
- For the eradication of the *Helicobacter pylori* bacterium, the normal treatment period is 7 days.

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 skin blisters, liver problems and acute generalised 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 (affects 1 to 10 users in 100).
- 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 (affects 1 to 10 users in 100).
- Hepatitis (inflammation of the liver which may make you feel unwell, 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 100), which sometimes may lead to brain 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):

- Insomnia, 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, sleepiness
- Bronchitis, sinusitis
- Indigestion, dry mouth, belching
- Rash, redness of the skin
- Muscle pain, leg cramps, joint pain
- Urinary tract infection
- Chest pain, chills, 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
- Depression.

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 *H. pylori* eradication therapy, see the individual product information leaflets.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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, heavy, hydroxypropylcellulose, magnesium stearate.

Coating – 10 mg tablets:

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).

Coating – 20 mg tablets:

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), black iron oxide (E172).

Printing ink:

Shellac, black iron oxide (E172), propylene glycol, N-butyl alcohol, 2-propanol, purified water, industrial methylated spirit, ethanol 96%.

What Rabeprazole Sodium looks like and contents of the pack

- Rabeprazole Sodium 10 mg Gastro resistant Tablets are pink, round tablets, imprinted on one side of the tablet with black ink "N" and "10".
- Rabeprazole Sodium 20 mg Gastro resistant Tablets are yellow, round tablets, imprinted in black ink with "93" on one side and "64" on the other.
- Rabeprazole sodium gastro-resistant tablets are available in pack sizes of 1, 7, 14, 15, 20, 25, 28, 30, 50, 56, 57, 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.

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

This leaflet was last revised in October 2010.

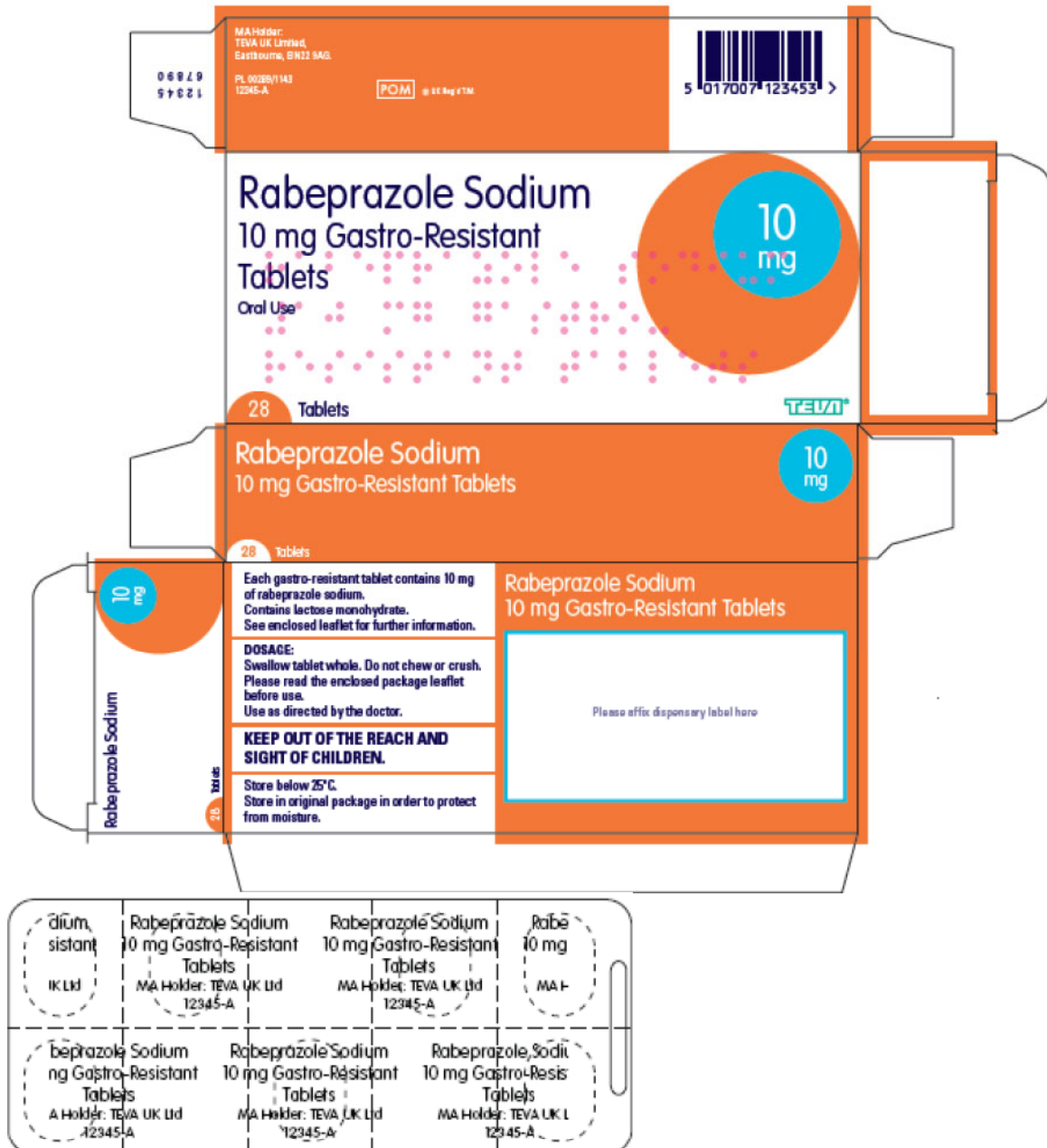
PL 00289/1143-1144



52315-A
160 x 323

Module 4 Labelling

Carton





<p>dium, sistant</p> <p>IK Ltd</p>	<p>Rabepazole Sodium 20 mg Gastro-Resistant Tablets</p> <p>MA Holder: TEVA UK Ltd 12345-A</p>	<p>Rabepazole Sodium 20 mg Gastro-Resistant Tablets</p> <p>MA Holder: TEVA UK Ltd 12345-A</p>	<p>Rabepazole Sodium 20 mg</p> <p>MA Holder: TEVA UK Ltd 12345-A</p>
<p>rabepazole Sodium 20 mg Gastro-Resistant Tablets</p> <p>MA Holder: TEVA UK Ltd 12345-A</p>	<p>Rabepazole Sodium 20 mg Gastro-Resistant Tablets</p> <p>MA Holder: TEVA UK Ltd 12345-A</p>	<p>Rabepazole Sodium 20 mg Gastro-Resistant Tablets</p> <p>MA Holder: TEVA UK Ltd 12345-A</p>	

Module 5

Scientific discussion during initial procedure

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 sulfenamides 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)	Rabepazole Sodium 10 mg Gastro-resistant Tablets Rabepazole Sodium 20 mg Gastro-resistant Tablets
Name(s) of the active substance(s) (INN)	Rabepazole sodium
Pharmacotherapeutic classification (ATC code)	A02B C04
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

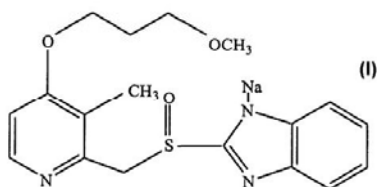
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN Rabeprazole sodium

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

Structure:



Empirical formula:

$C_{18}H_{20}N_3O_3SNa$

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 Pharmacopoeia (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)- 20msg 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/poylamide), 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_{max} , AUC_t and AUC_{∞} .

Statistical methods

Analysis of variance (ANOVA) would be performed on natural log-transformed pharmacokinetic parameters C_{max} , AUC_{∞} and AUC_t .

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)

Treatment	AUC_t ng/ml/h	AUC_{∞} ng/ml	C_{max} ng/ml
Test	696.18	705.66	437.28
Reference	743.54	753.69	478.03

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

Variable	Geometric mean	Confidence limits	Intra-individual CV (%)
AUC_t (ratio test/reference)	93.63	88.89 – 98.63	20.2 (A) 18.9 (B)
AUC_{∞} (ratio test/reference)	93.63	89.09 – 98.40	19.3 (A) 17.5 (B)
C_{max} (ratio test/reference)	91.48	83.84 – 99.81	42.3 (A) 29.4 (B)

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 AUC_t , AUC_{∞} and C_{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 rabepazole 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_{max} , AUC_t and AUC_{∞} .

Statistical methods

Analysis of variance (ANOVA) would be performed on natural log-transformed pharmacokinetic parameters C_{max} , AUC_{∞} and AUC_t .

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 Rabepazole 20mg –geometric mean (n=48)

Treatment	AUC_t ng/ml/h	AUC_{∞} ng/ml	C_{max} ng/ml
Test	474.33	477.17	261.47
Reference	464.72	474.54	246.07

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

Variable	Geometric mean	Confidence limits	Intra-individual CV (%)
AUC_t (ratio test/reference)	102.07	93.89 – 110.96	36.1 (A) 34.1 (B)
AUC_{∞} (ratio test/reference)	100.55	92.72 – 109.05	34.5 (A) 31.5 (B)
C_{max} (ratio test/reference)	106.26	92.01 – 122.72	57.9 (A) 68.4 (B)

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_t , AUC_{∞} and C_{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.

Pharmacokinetic conclusion

Bioequivalence studies submitted for Rabepazole 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_{max} , AUC_t and AUC_{∞} fall within the acceptance criteria of 80 – 125% in-line with the current guidelines.

Satisfactory justification is provided for a bio-waiver for Rabepazole Sodium 10mg Gastro-

resistant Tablets. As Raberprazole 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 used 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 Raberprazole 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 (Raberprazole 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 Raberprazole 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 Raberprazole 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 Raberprazole 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

Date submitted	Application type	Scope	Outcome
16 July 2012	Medical Variation Type 1B	To delete, the therapeutic indication, for eradication of <i>Helicobacter pylori</i> 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.	Approved

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 administrationAdults/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)