RABEPRAZOLE 10 MG AND 20 MG GASTRO-RESISTANT TABLETS

PL 24668/0253-6

UKPAR

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LAY SUMMARY

On 27th January 2012, the MHRA granted Caduceus Pharma Limited Marketing Authorisations (licences) for Rabeprazole 10 mg and 20 mg gastro-resistant tablets.

Rabeprazole 10 mg and 20 mg gastro-resistant tablets contain the active ingredient, Rabeprazole sodium.

Rabeprazole sodium acts by reducing the amount of acid made by the stomach.

Rabeprazole 10 mg and 20 mg gastro-resistant tablets are used to treat:

• Ulcer in the upper part of the intestine (duodenal ulcer) and benign stomach ulcer.

• Gastro-oesophageal reflux disease (GORD) with or without ulcer. GORD is commonly referred to as inflammation of the gullet caused by acid and associated with heartburn. Heartburn is a burning feeling rising from the stomach or lower chest up towards the neck. Rabeprazole 10 mg and 20 mg gastro-resistant tablets may also be used as a long term treatment of GORD (GORD maintenance). Rabeprazole 10 mg and 20 mg gastro-resistant tablets may also be used for the symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD).

• Zollinger-Ellison Syndrome, which is a condition when the stomach makes extremely high amounts of acid.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Rabeprazole 10 mg and 20 mg gastro-resistant tablets outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Caduceus Pharma Limited Marketing Authorisations for the medicinal products Rabeprazole 10 mg and 20 mg gastro-resistant tablets (PL 24668/0253-6) on 27th January 2012.

Rabeprazole 10 mg and 20 mg gastro-resistant tablets are prescription only medicines (POM) and are indicated for Rabeprazole tablets are 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

These applications for Rabeprazole 10 mg and 20 mg gastro-resistant tablets are submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Pariet 10 mg and 20 mg gastro-resistant tablets, authorised in the UK to Eisai Limited on 8th May 1998 (PL 10555/0010 & 0008 respectively).

Rabeprazole sodium is a proton pump inhibitor (PPI) and belongs to the class of anti-secretory 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). Rabeprazole blocks the final step of gastric acid secretion. The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

The pharmacovigilance system as described by the Marketing Authorisation Holder (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.

A Risk Management Plan was not submitted and one is not required for applications of this type.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Rabeprazole sodium monohydrate
INN: Rabeprazole (rabeprazole sodium monohydrate)

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

Structure:

Physical form: An off white to white crystalline powder.
Solubility: Very soluble in water and in methanol. Freely soluble in alcohol.
Molecular formula: C_{18}H_{20}N_{3}NaO_{3}S·H_{2}O
Molecular weight: 399.43

Rabeprazole sodium
INN: Rabeprazole (rabeprazole sodium)

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

Structure:

Physical form: A white to off white amorphous powder.
Solubility: Very soluble in water and in methanol. Freely soluble in alcohol
Molecular formula: C_{18}H_{20}N_{3}NaO_{3}S
Molecular weight: 381.43
There are two different polymorphic forms of the drug substance present in the drug product. The MAH justified this and have shown that they are interchangeable.

Rabeprazole sodium complies with in-house specifications.

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 specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof of structure data has been supplied for the drug substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Stability studies have been performed with the active substance and no significant changes of the parameters were observed. On the basis of the results, a suitable re-test period could be approved.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients in the tablet core are pharmaceutical excipients povidone, hydroxypropyl cellulose (low subst.), light magnesium oxide, mannitol (E421) and magnesium stearate.

The ingredients in the tablet undercoating are the pharmaceutical excipients ethyl cellulose and light magnesium oxide.

The ingredients in the tablet enteric coating are the pharmaceutical excipients methacrylic acid-ethyl acrylate copolymer, talc, polysorbate 80, sodium lauryl sulphate, propylene glycol, yellow iron oxide (E172) and titanium dioxide (E171)

Rabeprazole 10 mg gastro-resistant tablets have the extra excipient, red iron oxide (E172).

With the exception of hydroxypropyl cellulose (low subst.), yellow iron oxide (E172) and red iron oxide (E172), all the ingredients comply with their relevant European Pharmacopoeia monographs. Hydroxypropyl cellulose (low subst.), yellow iron oxide (E172) and red iron oxide (E172) comply with the United States Pharmacopoeia – National Formulary.

None of the excipients used contain material of animal or human origin. Confirmation has been provided that the magnesium stearate used in this product is of plant origin.
Pharmaceutical Development
The objective of the development programme was to produce safe, efficacious products containing rabeprazole sodium that could be considered generic medicinal products of Pariet 10 mg and 20 mg gastro-resistant tablets.

Suitable product development information has been provided. Valid justifications for the use and amounts of each excipient have been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products.

Comparative impurity profiles of the products containing different polymorphic forms of the active substance have been provided.

The reference products used in the bioequivalence studies are:
- Pariet 20 mg magensaftresistente tabletten (gastro-resistant tablets) which were authorised in Germany to Eisai GmbH.
- Pariet 20 mg gastro-resistant tablets which were authorised in Sweden to Eisai AB. These products are considered to be pharmaceutically equivalent to the UK reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. In-process controls are satisfactory based on batch data and controls on the finished products. Process validation data on batches of both strengths have been provided and are satisfactory.

A commitment to perform process validation on commercial-scale batches of both strengths has been provided.

Finished Product Specification
The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The products are packaged in:

i) Aluminium blister packs. Pack sizes are: 1, 5, 7, 14, 15, 20, 25, 28, 30, 50, 56, 60, 75, 98, 100 and 120 tablets.

ii) High-density polyethylene (HDPE) tablet containers with low-density polyethylene (LDPE) lids (and dessicant). Pack sizes are 30, 100 and 250 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation.
Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 24 months with the following satisfactory storage instructions:

i) Aluminium blister packs: Store below 25°C. Store in the original package in order to protect from moisture.

ii) HDPE tablet containers. Store below 25°C. Keep the container tightly closed in order to protect from moisture.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved SmPCs, PIL and label (text only) are included in modules 2, 3 and 4 of this report.

User testing results have been submitted for a typical PIL for this product. 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 it contains.

MAA Forms
These are pharmaceutically satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

The pharmacodynamics, pharmacokinetics and toxicological properties of rabeprazole sodium are well-known. As rabeprazole sodium is a widely used, well-known active substance, no new non-clinical data have been provided and none are required. An overview based on literature is therefore appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification for the absence of an Environmental Risk Assessment was provided.

From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, two bioequivalence studies have been provided, one under fed and one under fasted conditions:

Study 1

A randomised, open-label, two-treatment, two period, two sequence, single dose, crossover bioequivalence study comparing the pharmacokinetics of Rabeprazole 20 mg gastro-resistant tablets (Test) versus Pariet (rabeprazole sodium) 20mg magensaftrzistente tabletten (Eisai GmbH) (Reference) in healthy volunteers under fed conditions.

Blood sampling was performed pre-dose and up to 30 hours post dose in each treatment period. There was a washout period of 7 days. Pharmacokinetic parameters were calculated and statistically analysed.

Results from this study are presented below as log-transformed values:

### Geometric Least Mean Squares and 90% Confidence Interval

#### Pharmacokinetic parameters of rabeprazole sodium

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.hr/ml)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.hr/ml)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
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<tbody>
<tr>
<td>Test</td>
<td>900.364</td>
<td>903.168</td>
<td>504.593</td>
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<tr>
<td>Reference</td>
<td>942.249</td>
<td>956.702</td>
<td>549.834</td>
</tr>
<tr>
<td>Ratio</td>
<td>0.96</td>
<td>0.96</td>
<td>0.92</td>
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<tr>
<td></td>
<td>0.90 – 1.02</td>
<td>0.91 – 1.02</td>
<td>0.83 – 1.02</td>
</tr>
</tbody>
</table>

- **AUC<sub>0-t</sub>** area under the plasma concentration-time curve from time zero to t hours
- **AUC<sub>0-∞</sub>** area under the plasma concentration-time curve from time zero to infinity
- **C<sub>max</sub>** maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC<sub>0-t</sub> and C<sub>max</sub> for rabeprazole sodium lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference products under fed conditions.

Study 2

A randomised, open-label, two-treatment, four period, two sequence, single dose, fully replicate crossover bioequivalence study comparing the pharmacokinetics of Rabeprazole 20 mg gastro-resistant tablets (Test) versus Pariet (rabeprazole sodium) 20mg gastro-resistant tablets (Eisai AB, Sweden) (Reference) in healthy volunteers under fasted conditions.

Blood sampling was performed pre-dose and up to 24 hours post dose in each treatment period. There was a washout period of 4 days. Pharmacokinetic parameters were calculated and statistically analysed.
Results from this study are presented below as log-transformed values:
Geometric Least Mean Squares and 90% Confidence Interval

Pharmacokinetic parameters of rabeprazole sodium

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ (ng.hr/ml)</th>
<th>AUC$_{0-\infty}$ (ng.hr/ml)</th>
<th>C$_{max}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>1397.192</td>
<td>1425.173</td>
<td>623.885</td>
</tr>
<tr>
<td>Test 2</td>
<td>1370.351</td>
<td>1431.142</td>
<td>662.499</td>
</tr>
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<td>Reference 1</td>
<td>1246.914</td>
<td>1283.855</td>
<td>548.577</td>
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<td>Reference 2</td>
<td>1385.091</td>
<td>1418.299</td>
<td>667.320</td>
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<td>Ratio (90% CI)</td>
<td>1.06</td>
<td>1.07</td>
<td>1.07</td>
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<td>1.01 – 1.12</td>
<td>1.02 – 1.12</td>
<td>0.97 – 1.18</td>
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</table>

AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C$_{max}$ maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC$_{0-t}$ and C$_{max}$ for rabeprazole sodium lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference products under fasted conditions.

As the 20 mg tablet strength meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), the results and conclusions of the bioequivalence studies on the 20 mg tablet strength can be extrapolated to Rabeprazole 10 mg gastro-resistant tablets.

**Efficacy**
These are generic applications based on demonstration of bioequivalence and new data relating to efficacy are not required as per EU legislation once bioequivalence has been demonstrated.

**Safety**
These are generic applications based on demonstration of bioequivalence and new data relating to safety are not required as per EU legislation once bioequivalence has been demonstrated.

**Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling**
The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products.

**MAA Forms**
The MAA forms are clinically satisfactory.

**Clinical Overview**
The clinical overview has been written by a suitably qualified person and is satisfactory.
Conclusion
The bioequivalence studies has shown that Rabeprazole 10 mg and 20 mg gastro-resistant tablets can be considered as generic medicinal products to the reference products Pariet 10 mg and 20 mg gastro-resistant tablets.

From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
OVERALL CONCLUSIONS AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Rabeprazole 10 mg and 20 mg 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.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Rabeprazole 20 mg gastro-resistant tablets and the reference product, Pariet 20 mg gastro-resistant tablets. This conclusion can be extrapolated to Rabeprazole 10 mg gastro-resistant tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the reference products are interchangeable. Clinical experience with rabeprazole sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Applications on 5\textsuperscript{th} May 2009.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 8\textsuperscript{th} June 2009.</td>
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<tr>
<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the quality dossier on 11\textsuperscript{th} September 2009, 12\textsuperscript{th} August 2010 and 23\textsuperscript{rd} February 2011. The MHRA requested further information relating to the clinical dossier on 12\textsuperscript{th} August 2010.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 26\textsuperscript{th} May 2010, 17\textsuperscript{th} November 2010 and 14\textsuperscript{th} June 2011 for the quality section. The applicant responded to the MHRA’s requests, providing further information on 10\textsuperscript{th} January 2011 for the clinical section.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 27\textsuperscript{th} January 2012. The applications were completed on 27\textsuperscript{th} January 2012.</td>
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RABEPRAZOLE 10 MG AND 20 MG GASTRO-RESISTANT TABLETS

PL 24668/0253-6

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Rabeprazole 10 mg gastro-resistant tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Rabeprazole 10 mg gastro-resistant tablets contain rabeprazole sodium 10 mg corresponding to 9.42 mg rabeprazole.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.
Pink, coated, elliptical, biconvex tablet.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Rabeprazole tablets are 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 Rabeprazole 20 mg or 10 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 tablets should be taken in the morning before eating; and although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.

Patients should be cautioned that the Rabeprazole 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 the Use of Rabeprazole in the treatment of patients with severe hepatic impairment.

**Children**

Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

### 4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients used in the formulation.
- Pregnancy.
- 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.

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 inhibitor or substituted benzimidazoles cannot be excluded.

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

Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

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

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

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

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

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

### 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.

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

Co-administration of atazanavir 300 mg/ritonavir 10mg 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 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rabeprazole 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 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 would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8 UNDESIRABLE EFFECTS

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketed experience.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) 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>
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<tbody>
<tr>
<td>Infections and infestations</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
<td>Leucopenia</td>
<td>Thrombocytopenia</td>
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<td>Immune system disorders</td>
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<td>Bronchitis Sinusitis</td>
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<td>Pruritus Sweating Bullous reactions²</td>
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<td>Gynecomastia</td>
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<td>Increased hepatic enzymes³</td>
<td>Weight increased</td>
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¹ Includes facial swelling, hypotension and dyspnoea

² Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.

³ Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole 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: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors. ATC code: A02B C04

Mechanism of Action: Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or 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 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 \(283 ± 98\, \text{ml/min}\). 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 vivo studies may not always be predictive of in vitro 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 \(^{14}\text{C}\) 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 \(≤5\, \text{ml/min/1.73 m}^2\)), 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

**Tablet core:**
- Povidone
- Hydroxypropyl cellulose, low subst.
UKPAR Rabeprazole 10 mg and 20 mg Gastro-resistant Tablets

Magnesium oxide, light
Mannitol (E421)
Magnesium stearate

**Undercoating:**
Ethyl cellulose
Magnesium oxide, light

**Enteric coating:**
Methacrylic acid-ethyl acrylate copolymer
Talc
Polysorbate 80
Sodium lauryl sulphate
Propylene glycol
Iron oxide yellow (E172)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 **INCOMPATIBILITIES**
Not applicable.

6.3 **SHELF LIFE**
24 months

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**
Blisters: Store below 25°C. Store in the original package in order to protect from moisture.

Tablet containers: Store below 25°C. Keep the container tightly closed in order to protect from moisture.

6.5 **NATURE AND CONTENTS OF CONTAINER**

*Pack sizes:*
Blisters (aluminium/aluminium): 1, 5, 7, 14, 15, 20, 25, 28, 30, 50, 56, 60, 75, 98, 100 and 120 tablets.
HDPE tablet containers with LDPE lid (and a desiccant): 30, 100 and 250 tablets.

Not all pack sizes may be marketed.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street
London W1U 3RF
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 24668/0253

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
27/01/2012

10 **DATE OF REVISION OF THE TEXT**
27/01/2012
NAME OF THE MEDICINAL PRODUCT
Rabeprazole 20 mg gastro-resistant tablets.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Rabeprazole 20 mg gastro-resistant tablets contain rabeprazole sodium 20 mg corresponding to 18.85 mg rabeprazole.

For a full list of excipients, see 6.1.

PHARMACEUTICAL FORM
Gastro-resistant tablet.
Yellow, coated, elliptical, biconvex tablet.

CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Rabeprazole tablets are 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 Rabeprazole 20 mg or 10 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 tablets should be taken in the morning before eating; and although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.
Patients should be cautioned that the Rabeprazole 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 the Use of Rabeprazole in the treatment of patients with severe hepatic impairment.

Children
Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

4.3 CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients used in the formulation.
- Pregnancy.
- 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.

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 inhibitor or substituted benzimidazoles cannot be excluded.

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

Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

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

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

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

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

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

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

Co-administration of atazanavir 300 mg/ritonavir 10mg 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 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rabeprazole 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 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 would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8 UNDESIRABLE EFFECTS

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketed experience.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data)

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**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 ≤ 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

**Tablet core:**

- Povidone
- Hydroxypropyl cellulose, low subst.
- Magnesium oxide, light
- Mannitol (E421)
- Magnesium stearate
Undercoating:
Ethyl cellulose
Magnesium oxide, light

Enteric coating:
Methacrylic acid-ethyl acrylate copolymer
Talc
Polysorbate 80
Sodium lauryl sulphate
Propylene glycol
Iron oxide yellow (E172)
Titanium dioxide (E171)

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Blisters packs: Store below 25°C. Store in the original package in order to protect from moisture.

Tablet containers. Store below 25°C. Keep the container tightly closed in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Pack sizes:
Blisters packs (aluminium/aluminium): 1, 5, 7, 14, 15, 20, 25, 28, 30, 50, 56, 60, 75, 98, 100 and 120 tablets.
HDPE tablet containers with LDPE lid (and a desiccant): 30, 100 and 250 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street
London W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0254

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/01/2012

10 DATE OF REVISION OF THE TEXT
27/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Rabeprazole 10 mg gastro-resistant tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Rabeprazole 10 mg gastro-resistant tablets contain rabeprazole sodium 10 mg corresponding to 9.42 mg rabeprazole.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.
Pink, coated, elliptical, biconvex tablet.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Rabeprazole tablets are 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 Rabeprazole 20 mg or 10 mg once daily can be used depending upon patient response.

Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD): 20 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 tablets should be taken in the morning before eating; and although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.
Patients should be cautioned that the Rabeprazole 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 the Use of Rabeprazole in the treatment of patients with severe hepatic impairment.

**Children**

Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

### 4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients used in the formulation.
- Pregnancy.
- 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.

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 inhibitor or substituted benzimidazoles cannot be excluded.

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

Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

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

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

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

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

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

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

Co-administration of atazanavir 300 mg/ritonavir 10mg 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 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rabeprazole 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 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 would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8 UNDESIRABLE EFFECTS

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketed experience.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) 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>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Neutropenia</td>
<td>Leucopenia</td>
<td>Thrombocytopenia</td>
<td>Leucocytosis</td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Anorexia</td>
<td></td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Nervousness</td>
<td>Depression</td>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
<td>Somnolence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>Visual disturbance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Vascular disorders
- Cough
- Pharyngitis
- Rhinitis

### Respiratory, thoracic and mediastinal disorders
- Bronchitis
- Sinusitis

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

### Hepatobiliary disorders
- Hepatitis
- Jaundice
- Hepatic encephalopathy

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

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

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

### Reproductive system and breast disorders

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

### Investigations
- Increased hepatic enzymes
- Weight increased

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1 Includes facial swelling, hypotension and dyspnoea

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

3 Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole 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: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors. ATC code: A02B C04

Mechanism of Action: Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or 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 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 ciclosporin. 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
Tablet core:
- Povidone
- Hydroxypropyl cellulose, low subst.
- Magnesium oxide, light
- Mannitol (E421)
- Magnesium stearate

Undercoating:
Ethyl cellulose
Magnesium oxide, light

**Enteric coating:**
Methacrylic acid-ethyl acrylate copolymer
Talc
Polysorbate 80
Sodium lauryl sulphate
Propylene glycol
Iron oxide yellow (E172)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 **INCOMPATIBILITIES**
Not applicable.

6.3 **SHELF LIFE**
24 months

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**
Blisters: Store below 25°C. Store in the original package in order to protect from moisture.

Tablet containers. Store below 25°C. Keep the container tightly closed in order to protect from moisture.

6.5 **NATURE AND CONTENTS OF CONTAINER**
*Pack sizes:*
Blisters (aluminium/aluminium): 1, 5, 7, 14, 15, 20, 25, 28, 30, 50, 56, 60, 75, 98, 100 and 120 tablets.
HDPE tablet containers with LDPE lid (and a desiccant): 30, 100 and 250 tablets.

Not all pack sizes may be marketed.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street
London W1U 3RF
United kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 24668/0255

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
27/01/2012

10 **DATE OF REVISION OF THE TEXT**
27/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Rabeprazole 20 mg gastro-resistant tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Rabeprazole 20 mg gastro-resistant tablets contain rabeprazole sodium 20 mg corresponding to 18.85 mg rabeprazole.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.
Yellow, coated, elliptical, biconvex tablet.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Rabeprazole tablets are 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 Rabeprazole 20 mg or 10 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 tablets should be taken in the morning before eating; and although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.
Patients should be cautioned that the Rabeprazole 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 the Use of Rabeprazole in the treatment of patients with severe hepatic impairment.

**Children**
Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

### 4.3 CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients used in the formulation.
- Pregnancy.
- 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.

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 inhibitor or substituted benzimidazoles cannot be excluded.

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

Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

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

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

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

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

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

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

Co-administration of atazanavir 300 mg/ritonavir 10mg 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 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rabeprazole 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 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 would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8 UNDESIRABLE EFFECTS

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketed experience.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) 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>
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<tbody>
<tr>
<td>Infections and infestations</td>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Neutropenia</td>
<td>Leucopenia</td>
<td>Thrombocytopenia</td>
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<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity(^{1,2})</td>
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<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>Anorexia</td>
<td></td>
<td>Hyponatremia</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Nervousness</td>
<td>Depression</td>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
<td>Somnolence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td>Visual disturbance</td>
<td></td>
</tr>
</tbody>
</table>
### Vascular disorders
- Cough
- Pharyngitis
- Rhinitis
- Bronchitis
- Sinusitis
- Peripheral oedema

### Respiratory, thoracic and mediastinal disorders
- Diarrhoea
- Vomiting
- Nausea
- Abdominal pain
- Constipation
- Flatulence
- Cough
- Pharyngitis
- Rhinitis
- Bronchitis
- Sinusitis
- Gastritis
- Stomatitis
- Taste disturbance

### Gastrointestinal disorders
- Diarrhoea
- Vomiting
- Nausea
- Abdominal pain
- Constipation
- Flatulence
- Gastritis
- Stomatitis
- Taste disturbance

### Hepatobiliary disorders
- Hepatitis
- Jaundice
- Hepatic encephalopathy

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

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

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

### Reproductive system and breast disorders
- Gynecomastia

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

### Investigations
- Increased hepatic enzymes
- Weight increased

---

1. Includes facial swelling, hypotension and dyspnoea

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

3. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole 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

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors. ATC code: A02B C04

Mechanism of Action: Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or 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 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 ml/min/1.73 m²), 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 $t_{1/2}$ 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 $C_{\text{max}}$ 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

Tablet core:
- Povidone
- Hydroxypropyl cellulose, low subst.
- Magnesium oxide, light
- Mannitol (E421)
- Magnesium stearate
**Undercoating:**
- Ethyl cellulose
- Magnesium oxide, light

**Enteric coating:**
- Methacrylic acid-ethyl acrylate copolymer
- Talc
- Polysorbate 80
- Sodium lauryl sulphate
- Propylene glycol
- Iron oxide yellow (E172)
- Titanium dioxide (E171)

6.2 **INCOMPATIBILITIES**
Not applicable.

6.3 **SHELF LIFE**
24 months

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**
Blisters: Store below 25°C. Store in the original package in order to protect from moisture.

Tablets: Store below 25°C. Keep the container tightly closed in order to protect from moisture.

6.5 **NATURE AND CONTENTS OF CONTAINER**
**Pack sizes:**
- Blisters (aluminium/aluminium): 1, 5, 7, 14, 15, 20, 25, 28, 30, 50, 56, 60, 75, 98, 100 and 120 tablets.
- HDPE tablet containers with LDPE lid (and a desiccant): 30, 100 and 250 tablets.

Not all pack sizes may be marketed.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street
London W1U 3RF
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 24668/0256

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
27/01/2012

10 **DATE OF REVISION OF THE TEXT**
27/01/2012
Please note that there are no mock-ups available for PL 24668/0253-6 therefore the PILs shown are text only. The marketing authorisation holder has stated that it does not intend to market the products, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL mock-ups for PL 24668/0253-6 for review to the regulatory authority before marketing the products.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Rabeprazole 10 mg gastro-resistant tablets
Rabeprazole 20 mg gastro-resistant tablets
rabeprazole sodium

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

1. WHAT RABEPRAZOLE IS AND WHAT IT IS USED FOR

Rabeprazole belongs to a group of medicines called Proton Pump Inhibitors (PPIs). Rabeprazole acts by reducing the amount of acid made by the stomach.

Rabeprazole is used to treat:
- ulcer in the upper part of the intestine (duodenal ulcer) and benign stomach ulcer
- gastro-oesophageal reflux disease (GORD) with or without ulcer. GORD is commonly referred to as inflammation of the guttlet caused by acid and associated with heartburn. Heartburn is a burning feeling rising from the stomach or lower chest up towards the neck. Rabeprazole may also be used as a long term treatment of GORD (GORD maintenance). Rabeprazole may also be used for the symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD).
- Zollinger-Ellison Syndrome, which is a condition when the stomach makes extremely high amounts of acid.

2. BEFORE YOU TAKE RABEPRAZOLE

Do not take Rabeprazole
- if you are allergic (hypersensitive) to rabeprazole sodium or any of the other ingredients of Rabeprazole gastro-resistant tablets (listed in Section 6).
- if you are pregnant or breast feeding

Take special care with Rabeprazole
- if you are allergic to other proton pump inhibitors
- if you have or have had any liver problems
- if you are taking a medicine called atazanavir (used to treat HIV)

If the above applies to you, consult your doctor before using Rabeprazole.
Your doctor may perform or have performed an additional investigation called an endoscopy in order to diagnose your condition and/or exclude malignant disease. The possibility of stomach and oesophageal tumours should be excluded before treatment is started.

If you take Rabeprazole on a long-term basis (longer than 1 year) your doctor will probably monitor you regularly. You should report any new or different symptoms whenever you see your doctor.

Some abnormal blood values have been reported during treatment with Rabeprazole. Usually, the values become normal when the treatment is discontinued.

Rabeprazole is not recommended for use in children.

**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. This is especially important in case you are taking any of the following medicines:

- **atazanavir** (used to treat HIV); it is not recommended to take Rabeprazole if you are taking atazanavir
- **ketaconazole** or **itraconazole** (used to treat infections caused by a fungus)

**Pregnancy and breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine. Rabeprazole must not be used during pregnancy and breast-feeding.

**Driving and using machines**

It is unlikely that Rabeprazole would affect your ability to drive or operate machinery. However, occasionally rabeprazole can cause sleepiness. Therefore, driving and operating complex machinery should be avoided if you are affected.

3. **HOW TO TAKE RABEPRAZOLE**

Always take Rabeprazole exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is as follows:

**Adults and elderly**

*Duodenal ulcer and benign gastric ulcer*: 20 mg of Rabeprazole to be taken once daily in the morning. Most patients with duodenal ulcer are treated for four weeks and most patients with benign gastric ulcer are treated for six weeks. However a few patients may require additional treatment to achieve healing.

*Gastro-Oesophageal Reflux Disease (GORD) with ulcer*: 20 mg of Rabeprazole to be taken once daily for four to eight weeks.

**Long term treatment of GORD**: 10 mg or 20 mg of Rabeprazole once daily depending upon response.

**Symptomatic treatment of GORD**: 10 mg of Rabeprazole once daily for 4 weeks. Once symptoms have cleared your doctor may tell you to take 10 mg of Rabeprazole once daily when needed for subsequent symptom control.

*Zollinger-Ellison Syndrome*: 60 mg of Rabeprazole once a day to start with. The dose may then be adjusted by your doctor depending on how you respond to the treatment. Your doctor will tell you how many tablets to take and when to take them.

**Children**

Rabeprazole is not recommended for use in children.

**Instructions for use**
The tablets must be swallowed whole with half a glass of water and may not be chewed or crushed. When Rabeprazole is taken once daily, the tablets should be taken in the morning before breakfast.

**If you take more Rabeprazole than you should**
If you have taken more Rabeprazole than prescribed by your doctor, seek medical advice.

**If you forget to take Rabeprazole**
Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember. If it is almost time to take the next dose, wait until then. Do not take a double dose to make up for a forgotten dose.

4. **POSSIBLE SIDE EFFECTS**

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

**If you notice any of the following serious side effects, stop taking Rabeprazole and contact a doctor immediately:**
- Sudden wheezing, swelling of your lips, face or body, rash, fainting or difficulties swallowing (severe allergic reaction).
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.
- Reddening of the skin with blisters or peeling and may be associated with a high fever and joint pains. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis.

The frequency of possible side effects listed below is defined using the following convention:

- **Very common:** affects more than 1 user in 10
- **Common:** affects 1 to 10 users in 100
- **Uncommon:** affects 1 to 10 users in 1,000
- **Rare:** affects 1 to 10 users in 10,000
- **Very rare:** affects less than 1 user in 10,000
- **Not known:** frequency cannot be estimated from the available data

**Common:**
- cough, sore throat (inflammation of the pharynx), running nose
- nausea, vomiting, abdominal pain, diarrhoea, constipation, wind (flatulence)
- back pain, non-specific pain
- weakness or loss of strength, flu like symptoms
- sleeplessness
- headache, dizziness
- infection

**Uncommon:**
- nervousness
- sleepiness
- inflammation of the bronchial tubes (bronchitis), inflammation of the sinuses (sinusitis)
- indigestion, dry mouth, belching
- rash, skin redness (erythema)
- muscle pains, joint pains, leg cramps
- urinary tract infection
- chest pain, chills, fever
- increased liver enzymes, which is measured by blood tests

**Rare:**
- blood problems such as reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- increased number of white blood cells
- allergic reactions including facial swelling, low blood pressure and breathing difficulties
- loss of appetite
- depression
- visual disturbance
- inflammation of the stomach, inflammation of the mouth, taste disturbance
- inflammation of the liver, jaundice (yellowing of the skin or eyes), brain disturbance associated with liver failure (hepatic encephalopathy)
- itching, sweating, skin blisters
- kidney inflammation (interstitial nephritis)
- increased weight

Very rare:
- sudden onset of severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN))

Not known
- low levels of sodium in the blood
- confusion
- swelling of the feet and ankles
- enlarged breasts in men

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**

Keep out of the reach and sight of children.

Blister packs: Store below 25°C. Store in the original package in order to protect from moisture.

Tablet containers: Store below 25°C. Keep the container tightly closed in order to protect from moisture.

Do not use Rabeprazole after the expiry date which is stated on the carton and label/blister after Expiry Date/Exp. 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 gastro-resistant tablets contain**

- The active substance is rabeprazole sodium. Each tablet contains 10 mg or 20 mg rabeprazole sodium.
- The other ingredients are:
  - core: povidone, mannitol (E421), light magnesium oxide, low substituted hydroxypropyl cellulose, magnesium stearate;
  - sealing: ethyl cellulose, light magnesium oxide;
  - gastro-resistant coating: methacrylic acid-ethyl acrylate copolymer, polysorbate 80, sodium lauryl sulphate, propylene glycol, talc, iron oxide red (E172) iron oxide yellow (E172) titanium dioxide (E171)

**What Rabeprazole gastro-resistant tablets look like and contents of the pack**
Rabeprazole 10 mg gastro-resistant tablet: Pink, coated, elliptical, biconvex tablet.
Rabeprazole 20 mg gastro-resistant tablet: Yellow, coated, elliptical, biconvex tablet.

Pack sizes:
Blisters packs (aluminium/aluminium): 1, 5, 7, 14, 15, 20, 25, 28, 30, 50, 56, 60, 75, 98, 100 and 120 tablets
Plastic tablet containers with a desiccant: 30, 100 and 250 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street
London W1U 3RF
United kingdom

Manufacturer:
Actavis hf
Reykjavikurvegi 78
P.O.Box 420
1S-220 Hafnarfjordur
Iceland

This leaflet was last updated in 01/2012.
Please note that there are no mock-ups available for PL 24668/0253-6, therefore the labelling shown is the labelling text only. The marketing authorisation holder has stated that it does not intend to market the products, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling mock-ups for PL 24668/0253-6 for review to the regulatory authority before marketing the products.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

- Carton for blister
- Carton for bottle
- Label for bottle

**1. NAME OF THE MEDICINAL PRODUCT**

Rabeprazole 10 mg gastro-resistant tablets

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One gastro-resistant tablet contains 10 mg rabeprazole sodium corresponding to 9.42 mg rabeprazole.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Gastro-resistant tablets.

1 tablet  
5 tablets  
7 tablets  
14 tablets  
15 tablets  
20 tablets  
25 tablets  
28 tablets  
30 tablets  
50 tablets  
56 tablets  
60 tablets  
75 tablets  
98 tablets  
100 tablets  
120 tablets  
250 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.  
The tablets should be swallowed whole.  
Do not chew or crush.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry date:

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

Blister Packs: Store in the original package in order to protect from moisture.
Tablet Containers: Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London W1U 3RF
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0253

13. BATCH NUMBER

Batch number:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cartons only: rabeprazole 10 mg gastro-resistant tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

<table>
<thead>
<tr>
<th>Blister foil</th>
</tr>
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1. **NAME OF THE MEDICINAL PRODUCT**

Rabeprazole 10 mg gastro-resistant tablets

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Caduceus Pharma Ltd

3. **EXPIRY DATE**

Exp:

4. **BATCH NUMBER**

Lot:

5. **OTHER**
UKPAR Rabeprazole 10 mg and 20 mg Gastro-resistant Tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blister
Carton for bottle
Label for bottle

1. NAME OF THE MEDICINAL PRODUCT

Rabeprazole 20 mg gastro-resistant tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gastro-resistant tablet contains 20 mg rabeprazole sodium corresponding to 18.85 mg rabeprazole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant tablets.

1 tablet
5 tablets
7 tablets
14 tablets
15 tablets
20 tablets
25 tablets
28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
75 tablets
98 tablets
100 tablets
120 tablets
250 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
The tablets should be swallowed whole.
Do not chew or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry date:

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

Blister Packs: Store in the original package in order to protect from moisture.

Tablet Containers: Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London W1U 3RF
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0254

13. BATCH NUMBER

Batch number:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cartons only: rabeprazole 20 mg gastro-resistant tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
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<tbody>
<tr>
<td>Blister foil</td>
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<table>
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<th>5. OTHER</th>
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</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blister
Carton for bottle
Label for bottle

1. NAME OF THE MEDICINAL PRODUCT

Rabeprazole 10 mg gastro-resistant tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gastro-resistant tablet contains 10 mg rabeprazole sodium corresponding to 9.42 mg rabeprazole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant tablets.

1 tablet
5 tablets
7 tablets
14 tablets
15 tablets
20 tablets
25 tablets
28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
75 tablets
98 tablets
100 tablets
120 tablets
250 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
The tablets should be swallowed whole.
Do not chew or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.
7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   Expiry date:

9. **SPECIAL STORAGE CONDITIONS**

   Store below 25°C.

   *Blister Packs*: Store in the original package in order to protect from moisture.
   *Tablet Containers*: Keep the container tightly closed in order to protect from moisture.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

    Caduceus Pharma Limited
    6th Floor
    94 Wigmore Street
    London W1U 3RF
    United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

    PL 24668/0255

13. **BATCH NUMBER**

    Batch number:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

    *POM*

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

   *Cartons only*: rabeprazole 10 mg gastro-resistant tablets
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blister
Carton for bottle
Label for bottle

1. NAME OF THE MEDICINAL PRODUCT

Rabeprazole 20 mg gastro-resistant tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gastro-resistant tablet contains 20 mg rabeprazole sodium corresponding to 18.85 mg rabeprazole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant tablets.

1 tablet
5 tablets
7 tablets
14 tablets
15 tablets
20 tablets
25 tablets
28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
75 tablets
98 tablets
100 tablets
120 tablets
250 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
The tablets should be swallowed whole.
Do not chew or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.
7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

Expiry date:

9. **SPECIAL STORAGE CONDITIONS**

Store below 25°C.

*Blister Packs:* Store in the original package in order to protect from moisture.

*Tablet Containers:* Keep the container tightly closed in order to protect from moisture.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Caduceus Pharma Limited  
6th Floor  
94 Wigmore Street  
London W1U 3RF  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 24668/0256

13. **BATCH NUMBER**

Batch number:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[POM]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

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