
Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)**RABEZOL®***Rabeprazole sodium***1.1. Strength**

Rabeprazole sodium 20 mg (equivalent to 18,85 mg of rabeprazole)

1.2. Pharmaceutical form

Gastro-resistant tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION**2.1. Qualitative declaration**

Rabeprazole sodium

For full list of excipients, see section 6.1.

2.2. Quantitative declaration

Each gastro-resistant tablet contains 20 mg of rabeprazole sodium, equivalent to 18,85 mg of rabeprazole.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

Round, biconvex, yellow coloured, enteric coated tablet.

4. CLINICAL PARTICULARS**4.1. Therapeutic indications**

Rabezol is indicated for the treatment of

- Active duodenal ulcer
- Active benign gastric ulcer
- Symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD)

- Gastro-Oesophageal Reflux Disease Long-term Management (GORD maintenance)
- Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD)
- Zollinger Ellison Syndrome
- In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* in patients with peptic ulcer disease.

4.2. Posology and mode of administration

4.2.1. Posology adults and adolescents

- **Active Duodenal Ulcer and Active Benign Gastric Ulcer**

The recommended oral dose is 20 mg to be taken once daily in the morning. Most patients with active duodenal ulcer heal within 4 weeks. However a few patients may require an additional 4 weeks of therapy to achieve healing. Most patients with active benign gastric ulcer heal within 6 weeks. However again a few patients may require an additional 6 week 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 4 to 8 weeks.

- **Gastro-Oesophageal Reflux Disease Long term management (GORD Maintenance)**

For long term management, a maintenance dose of Rabezol 20mg or of rabeprazole sodium 10mg once daily can be used depending upon patient response.

- **Symptomatic treatment of moderate to very severe Gastro-Oesophageal Reflux Disease (symptomatic GORD)**

In patients without oesophagitis: 10 mg rabeprazole sodium once daily. If symptoms control has not been achieved during 4 weeks, the patient should be further investigated. Once the 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 Rabezol once a day. The dose may be titrated upwards to 120 mg/day based on individual patient needs. Single daily doses up to 100 mg/day may be given. 120 mg dose may require divided doses, 60 mg twice daily. Treatment should continue for as long as clinically indicated.

- **Eradication of *H. pylori***

Patients with *H. pylori* infection should be treated with eradication therapy. The following combination given for 7 days is recommended. Rabezol 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily.

4.2.2. Special populations

Renal and hepatic impairment

No dosage adjustment is necessary for patients with renal or hepatic impairment. There are no clinical data on the use of rabeprazole in the treatment of patients with severe hepatic dysfunction: caution is advised when Rabezol is first initiated in such patients.

4.2.3. Pediatric population

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

4.2.4. Method of administration

For indications requiring once daily treatment Rabezol gastro-resistant tablets should be taken in the morning, before eating; and although neither the time of day nor food intake has shown to have any effect on Rabezol activity, this regimen will facilitate treatment compliance. Patient should be cautioned that the Rabezol gastro-resistant tablets should not be chewed or crushed; they should be swallowed whole.

4.3. Contraindications

- Rabazol is contra-indicated in patients with known hypersensitivity to rabeprazole, to derivatives of benzimidazole or to any excipient mentioned in section 6.1.
- Rabazol is contraindicated in pregnancy and during breast feeding.

4.4. Special warning and precautions for use

4.4.1. General information

Symptomatic response to therapy with Rabazol does not exclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with Rabazol.

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

Because there are no clinical data on the use of Rabazol in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabazol is first initiated in such patients.

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

There have been post marketing reports of blood dyscrasias (thrombocytopenia and neutropenia). Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported since rabeprazole products are marketed.

In the majority of the cases where an alternative etiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

4.4.2. Pediatric population

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

4.5. Interactions with other medicinal products and other forms of interactions

4.5.1. General information

Cytochrome P450 System

Rabeprazole, a proton pump inhibitor (PPI), like other members of this class of medicines, is metabolised via hepatic cytochrome P450 (CYP450) system drug metabolism. Specifically, studies with human liver microsomes, show that rabeprazole is metabolised by CYP3A4 and CYP2C19 isoenzymes.

In studies conducted in healthy subjects it is shown that rabeprazole doesn't interact in a clinically significant way with warfarin, phenytoin, theophylline, or diazepam and the other drugs which are metabolised by CYP450 system.

Antibacterial combination therapy

Combination therapy performed with the antimicrobial agents: four-arm crossover study, in 16 healthy volunteers with 20 mg of rabeprazole, 1000 mg, amoxicillin, 500 mg clarithromycin or a combination with these three agents, i.e., rabeprazole, amoxicillin and clarithromycin (RAC). During the combination therapy, clarithromycin and amoxicillin AUC and C_{max} values were found similar when compared with monotherapy. When compared with the data obtained during monotherapy, AUC and C_{max} values of rabeprazole increased 11% and 34% and AUC and C_{max} values of 14-hydroxy-clarithromycin (active clarithromycin metabolite) increased 42% and 46%. This increase to be exposed to rabeprazole and 14-hydroxy-clarithromycin was not found important.

Interferences due to inhibition of gastric acid secretion

Rabeprazole 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 with ketoconazole (decreasing of 30%) or itraconazole (increasing of 22%) 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.

Antacids

In clinical studies, antacids were used concomitantly with the administration of rabeprazole. Also, in a specific drug-drug interaction study, no interaction with liquid antacids (aluminium hydroxide gel or magnesium hydroxide) was observed.

Cyclosporine

Human liver microsomes are used in vitro (in a laboratory) incubations, rabeprazole, cyclosporine metabolism 62 micromole with an IC₅₀ inhibited revealed that, said this concentration for 14 days, 20 mg rabeprazole administered in healthy volunteers detected C_{max} 50 times higher. This degree of inhibition equivalent to that provided by at concentrations close to omeprazole.

Atazanavir

Co-administration of atazanavir 300mg/ritonavir 10 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other proton pump inhibitors. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir.

4.5.2. Additional information on special populations

No additional information available.

4.5.3. Pediatric population

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

4.6. Pregnancy, lactation and fertility

4.6.1. Pregnancy

There are no clinical 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, although foeto-placental transfer occurs in rats.

Rabeprazole gastro-resistant tablets are contraindicated during pregnancy.

4.6.2. Lactation

It is not known whether rabeprazole is excreted in human breast milk. No studies in lactating women have been performed. Rabeprazole is however excreted in rat mammary secretions.

Therefore Rabazol should not be used during breast feeding.

4.6.3. Fertility

Reproductive studies conducted in rats and rabbits do not show the deterioration in fertility due to rabeprazole.

4.7. Effects on the ability to drive and use machines

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that Rabazol 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 majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature. The most commonly reported adverse

drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea and nausea.

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

Frequencies are defined as: common ($>1/100$, $<1/10$), uncommon ($>1/1,000$, $<1/100$), rare ($>1/10,000$, $<1/1,000$) and very rare ($<1/10,000$)

System organ class/ Undesirable effect	Frequency
Infections and infestations	
Infections	Common
Blood and the lymphatic system	
Neutropenia, leucopenia, thrombocytopenia, leucocytosis	Rare
Immune system disorders	
Acute systemic allergic reactions (e.g. hypotension and dyspnoea)	Rare
Metabolism and nutrition disorders	
Anorexia	Rare
Hyponatremia	not known
Psychiatric disorders	
insomnia	Common
Nervousness	Uncommon
Depression	Rare
Confusion	Unknown
Nervous system disorders	
Headache, dizziness	Common
Somnolence	Uncommon
Vascular disorders	
Peripheral oedema	Unknown
Eye disorders	
Visual disturbance	Rare
Respiratory, thoracic and mediastinal disorders	

System organ class/ Undesirable effect	Frequency
Cough, pharyngitis, rhinitis	Common
Bronchitis, sinusitis	Uncommon
Gastrointestinal disorders	
Diarrhoea, vomiting, nausea Abdominal pain Constipation, flatulence	Common
Dyspepsia, dry mouth, eructation	Uncommon
Gastritis, stomatitis, taste disturbance	Rare
Hepato-biliary disorders	
Hepatitis, jaundice, hepatic encephalopathy	Rare
Skin and subcutaneous tissue disorders	
Rash, erythema	Uncommon
Pruritus, sweating, bullous reactions	Rare
Erythema multiforme, toxic epidermal necrolysis (TEN) Stevens-Johnson syndrome (SJS)	Very rare
Musculoskeletal, connective tissue and bone disorders	
Non-specific pain, back pain	Common
Myalgia, leg cramps, arthralgia	Uncommon
Renal and urinary disorders	
Urinary tract infection	Uncommon
Interstitial nephritis	Rare
Reproductive system and breast disorders	
Gynecomastia	Unknown
General disorders and administration site conditions	
Asthenia, influenza-like illness	Common
Chest pain, chills, pyrexia	Uncommon
Investigations	
Increased hepatic enzymes	Uncommon
Weight increase	Rare

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 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

Pharmaceutical group: proton pump inhibitor for peptic ulcer and gastro-oesophageal reflux disease (GORD).

ATC code : A02BC04

Mechanism of Action

Rabeprazole 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 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 cysteine on the proton pump.

Anti-secretory Activity

After oral administration of a 20 mg dose of rabeprazole the onset of the anti-secretory effect occurs within 1 hour, with the maximum effect occurring within 2 to 4 hours.

Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of rabeprazole are 69% and 82% respectively and the duration of inhibition lasts up to 48 hours. The inhibitory effect of rabeprazole on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after 3 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, 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.

Enterochromaphin like (ECL) Cell Effects

Eight weeks periods of rabeprazole and comparisons agent applied more than 500 patients taken from the antrum and fundus of the stomach biopsy specimens, ECL cell histology, degree of gastritis, atrophic gastric incidence of intestinal metaplasia or H. pylori. There was no change in the distribution of infection. Rabeprazole (10 or 20 mg / day) and up to 1 year, more than 400 patients undergoing treatment, with incidence of ECL hyperplasia and omeprazole (20 mg / day) were compared with those observed. Thirty-six months continuously monitored over 250 patients under treatment, no significant changes in the initial phase of the existing evidence has been found.

Other Effects

Systemic effects of rabeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Rabeprazole, 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 somatotropin hormone.

Studies in healthy subjects have shown that rabeprazole 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

Rabazol is an enteric-coated (gastro-resistant) tablet formulation of rabeprazole. 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 +3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) and AUC are linear over the dose range of 10mg to 40mg. Absolute bioavailability of an oral 20mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma half-life is +1 hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. Neither food nor the time of day of administration of the treatment affects the absorption of rabeprazole.

Distribution

Rabeprazole is approximately 97% bound to human plasma proteins.

Metabolism and excretion

Rabeprazole is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolising system. In vitro studies with human liver microsomes indicated that rabeprazole is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In these studies, at expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and although in vitro studies may not always be predictive of in vivo status these findings indicate that no interaction is expected between rabeprazole

and cyclosporin. In humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma.

Following a single 20 mg ¹⁴C labelled oral dose of rabeprazole, 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.

Linearity / non-linearity

Pharmacokinetics of rabeprazole are linear in rabeprazole 10 mg and 40 mg dose interval.

Additional data for special populations

- Gender: Adjusted for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single 20 mg dose of rabeprazole.
- Renal dysfunction: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance $\leq 5 \text{ ml/min/1.73m}^2$), 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 20mg dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there

was a 2-3 fold increase in half-life of rabeprazole compared to the healthy volunteers. However, following a 20mg dose daily for 7 days the AUC had increased to only 1.5-fold and the C_{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 20mg of rabeprazole, 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 20mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and t_{1/2} which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolisers whilst C_{max} had increased by only 40%.

5.3. Preclinical safety data

Non-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data.

Studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but in vivo micronucleus and in vivo and in vitro DNA repair tests were negative.

Carcinogenicity studies revealed no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core Tablet

Mannitol (E421)

Magnesium oxide

Hydroxypropylcellulose

Sodium starch glycolate

Magnesium stearate

Gastro-resistant coating layers

Hypromellose

Propylene glycol

Talc

Methacrylic acid ethylacetate copolymer 1:1, type A (Eudragit L 100/55)

Titanium dioxide (E171)

Yellow iron oxide (E172)

Macrogol (polyethylene glycol)

Triethyl citrate

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 25°C, in original package to protect from moisture.

6.5. Nature and contents of container

Cardboard box with 14 gastro-resistant, round, yellow tablets, packed in Al/Al foil blister, and a patient leaflet

6.6. Special precautions for disposal and other handlings

No special requirements

Any unused medicine or waste must be disposed of in accordance with the regulations in force.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland

7.2. Manufacturer

Bilim İlaç San.ve. Tic. A.Ş (Bilim Pharmaceuticals)

GOSB 41480 Gebze, Kocaeli, Turkey

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10 DATE OF REVISION OF TEXT

April 2019