Rabezol®

rabeprazole

INDICATIONS AND POSOLOGY	
ACTIVE DUODENAL ULCER	20 mg once daily in the morning.
ACTIVE BENIGN GASTRIC ULCER	20 mg taken once daily.
SYMPTOMATIC EROSIVE OR ULCERATIVE GASTRO-OESOPHAGEAL REFLUX DISEASE (GERD)	20 mg taken once daily
GASTRO-OESOPHAGEAL REFLUX DISEASE LONG-TERM MANAGEMENT (GERD MAINTENANCE)	A maintenance dose of **RABEZOL®** 20 mg (or 10 mg) once a day can be used depending on the patient response.
SYMPTOMATIC TREATMENT OF MODERATE TO VERY SEVERE GASTRO-OESOPHAGEAL REFLUX DISEASE (SYMPTOMATIC GERD)	The dose for patients who do not have esophagitis is 10 mg once a day.
ZOLLINGER-ELLISON SYNDROME	The recommended starting dose for adults is 60 mg once daily. The dose may optionally be increased up to 120 mg per day, depending on the individual patient's needs.
ERADICATION OF HELICOBACTER PYLORI	Eradication therapy: the following combination is recommended when administered for 7 days: **RABEZOL®** 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily.
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 **RABEZOL®** tablets should be taken in the morning, before eating. **RABEZOL®** tablets should not be chewed or crushed, but should be swallowed whole.	
RABEZOL® is not recommended for use in children, as there is no experience of its use in this group.	

DAFRA PHARMA INTERNATIONAL

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3FIRZOLE-2021

Dafra PHARMA

Setting the Standard

www.dafrapharma.com

Rabezol®

rabeprazole

EUROPEAN GMP

POWERFUL TREATMENT OF GASTRO-OESOPHAGEAL REFLUX AND ACTIVE GASTRO-DUODENAL ULCERS

DECREASE ACIDITY

RESTORE THE MUCUS LAYER

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Rabezol®

rabeprazole

PRESENTATION: Box of 14 capsules divided into two blister of 7. Each gastro-resitant tablet contains 20 mg of rabeprazole sodium equivalent to 18.85 mg of rabeprazole.

INDICATIONS:

Adults

- In the treatment of active duodenal ulcers
- In the treatment of active benign gastric ulcers
- In the treatment of symptomatic erosive or ulcerative gastro-oesophageal reflux disease (gerd)
- Gastro-oesophageal reflux disease long-term management (gerd maintenance)
- Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic gerd)
- In the treatment of the Zollinger-ellison syndrome
- In the eradication of helicobacter pylori

Children: **RABEZOL®** is not recommended for use in children, as there is no experience of its use in this group.

CONTRA-INDICATIONS: **RABEZOL®** is contra-indicated in patients with known hypersensitivity to rabeprazole sodium, substitute benzimidazoles or to any excipient used in the formulation. **RABEZOL®** is contra-indicated in pregnancy and during breast feeding.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

- Symptomatic response to therapy with **RABEZOL®** does not preclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with **RABEZOL®**.
- Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.
- Co-administration of atazanavir with **RABEZOL®** is not recommended.
- A risk of cross-hypersensitivity reactions with other proton pump inhibitor or 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 market authorization. In the majority of cases the events were uncomplicated and resolved on discontinuation of rabeprazole.

INTERACTION WITH OTHER MEDICINAL PRODUCTS: Rabeprazole sodium is metabolized via hepatic drug metabolism, specifically by CYP3A4 and CYP2C19 iso-enzymes. During combination therapy with clarithromycin and amoxicillin AUC and Cmax values were found similar when compared with monotherapy. When compared with the data obtained during monotherapy, AUC and Cmax values of rabeprazole increased 11% and 34% and AUC and Cmax values of 14-hydroxy-clarithromicycin (active clarithromycin metabolite) increased 42% and 46%. This increase to be exposed to Rabeprazole and 14-hydroxyclarithromicycin was not found important. Interferences due to inhibition of gastric acid secretion: Rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur. Coadministration 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 **RABEZOL®**. Antacids: No interaction with liquid antacids (aluminum hydroxide gel or magnesium hydroxide) was observed. Foods: Using low-fat foods a clinically significant interaction with food was observed. A high fat content of sodium rabeprazole with food application, can delay absorption of at least 4 hrs., but Cmax and absorbance (AUC) values have not changed. Coadministration with cyclosporine made the rabeprazole Cmax 50 times higher.
Co-administration of atazanavir 300mg/ritonavir 10 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Therefore rabeprazole should not be co-administered with atazanavir.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: It is unlikely that **RABEZOL®** 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.

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.

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. **RABEZOL®** is extensively protein bound and is, therefore, not dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

PHARMACODYNAMIC PROPERTIES: 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. 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 1 hr., with the maximum effect occurring within 2 to 4 hrs. Inhibition of basal and food stimulated acid secretion 23 hrs. after the first dose of rabeprazole sodium are 69% and 82% respectively and the duration of inhibition lasts up to 48 hrs. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after 3 days. When the drug is discontinued, secretory activity normalizes over 2 to 3 days.

PHARMACOKINETIC PROPERTIES: Absorption: **RABEZOL®** is an enteric-coated (gastro-resistant) tablet formulation of rabeprazole sodium. This is necessary because rabeprazole is acid-labile. Absorption therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels occurring + 3.5 hrs. after a 20 mg dose. Peak plasma concentrations (Cmax) 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 hr. (0.7 to 1.5 hrs.), 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 affect the absorption of rabeprazole sodium. Distribution: + 97% bound to human plasma proteins. Metabolism and excretion: Rabeprazole sodium is metabolized through the CYP450. No unchanged drug was excreted in the urine. + 90% of the dose was eliminated in urine mainly as 2 metabolites. The remainder of the dose was recovered in faeces. Linearity/non-linearity: Pharmacokinetics are linear. Additional data for special populations: Gender: there are no significant gender differences in pharmacokinetic parameters. Renal dysfunction: In patients with stable, end-stage, renal failure requiring maintenance hemodialysis (creatinine clearance ≤5ml/min/1.73m2), the disposition of rabeprazole was very similar to 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 Cmax to only 1.2-fold. The half-life of rabeprazole in patients with hepatic impairment was 12.3 hrs. compared to 2.1 hrs. 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. However there was no evidence of rabeprazole accumulation.

PHARMACEUTICAL PARTICULARS: List of excipients: Mannitol (E421) (67,0mg), Magnesium oxide, Hydroxypropyl cellulose, Sodium starch glycolate (5.0 mg), Magnesium stearate / **Excipients of coating:** Hypromellose, Propylene glycol (0.375 mg), Talc, Eudragit L 100/55, Titanium dioxide, Yellow iron oxide, Polyethylene glycol, Triethyl citrate. **Shelf life:** 2 years. **Special precautions for storage:** Store below 25°C in the original package in order to protect from moisture. **Legal status:** by prescription only.
MARKETING AUTHORISATION HOLDER: Dafra Pharma GmbH., Mühlenberg 7, 4052 Basel, Switzerland.
MANUFACTURER: Bilim Pharmaceuticals, GOSB 41480, Gebze-Kocaeli, Turkey.

For the complete SMPC, please visit www.dafrapharma.com