

Rabec[®]

Rabeprazole sodium

Coated tablets

MADE IN ARGENTINA - Rx only

Rabec 10 mg coated tablet

Rabec 20 mg coated tablet

FORMULA

Each coated tablet of Rabec[®] 10 mg contains:
Rabeprazole sodium 10 mg.
Inactive ingredients: mannitol 77.50 mg, heavy magnesium oxide 10 mg, hydroxypropyl cellulose 2.4 mg, croscarmellose sodium 6.10 mg, talc 9.69 mg, magnesium stearate 1 mg, Eudragit L/100 12.2525 mg, polyethylene glycol 6000 0.61 mg, yellow lacquer D&C N° 10 0.15 mg, sunset yellow lacquer N° 6 0.009 mg, titanium dioxide 3.0633 mg, triethylcitate 1.2252 mg.

Each coated tablet of Rabec[®] 20 mg contains:
Rabeprazole sodium 20 mg.
Inactive ingredients: mannitol 88.861 mg, heavy magnesium oxide 11.4644 mg, hydroxypropyl cellulose 3.0237 mg, croscarmellose sodium 7.6441 mg, talc 13.4324 mg, magnesium stearate 1.2 mg, Eudragit L/100 12.2525 mg, polyethylene glycol 6000 0.35 mg, yellow lacquer D&C N° 10 0.176 mg, sunset yellow lacquer D&C N° 6 0.017 mg, titanium dioxide 1.3469 mg, triethylcitate 1.2252 mg.

THERAPEUTIC ACTION

Antiulcer. Inhibitor of gastric acid secretion.
Code ATC: A02BC04.

INDICATIONS

Rabec[®] tablets are indicated for:
Treatment of active duodenal ulcer and active benign gastric ulcer.
Treatment of erosive or ulcerative symptomatic gastroesophageal reflux disease (GERD).
Maintenance treatment for GERD.
Treatment of moderate to severe symptomatic GERD.
Zollinger- Ellison syndrome.
Helicobacter pylori Eradication in patients with peptic ulcer, in combination with appropriate antibiotic therapy.

CLINICAL PHARMACOLOGY

Pharmacological action

Mechanism of Action: Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole) that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+, K+ATPase (proton pump). The effect is dose dependent and leads to inhibition of basal secretion and stimulated acid secretion. Animal studies indicate that after administration, Rabeprazole rapidly disappears from plasma and gastric mucosa. Being a weak base, Rabeprazole is rapidly absorbed and is concentrated in the acidic environment of the parietal cells. It is converted to its active sulfenamide form through proton binding and subsequently interacts with the cysteines available in the proton pump.

Antisecretory Activity: After oral administration of a dose of 20 mg of rabeprazole onset of action occurs within the first hour, reaching maximum

effect within 2 to 4 hours. The inhibition of basal secretion and secretion stimulated by food, 23 hours after the first dose of rabeprazole is 69% and 82% respectively. The inhibition lasts up to 48 hours. The inhibitory effect of Rabeprazole on acid secretion increases slightly with once a day repeated doses, reaching steady state after three days. After discontinuation of the drug, secretory activity returns to normal after 2 to 3 days.

Effects on Serum Gastrin: In clinical studies patients were treated with a dose of Rabeprazole 10 or 20 mg once daily for a period of up to 43 months of treatment. Serum gastrin increased during the first 2 to 8 weeks reflecting the inhibitory effect on acid secretion and remained stable during treatment. Serum gastrin levels returned to pre-treatment, usually within the first or second week after discontinuing it.

In biopsies of gastric antrum and fundus of more than 500 patients who received Rabeprazole or other drug of the group for a period of up to 8 weeks, there were no changes in the histology of Enterochromaffin-like (ECL) Cells, grade of gastritis, incidence of atrophic gastritis, intestinal metaplasia or infection distribution by *H. Pylori*. In over 250 patients followed for 36 months of continuous treatment, there were no significant changes from baseline.
Other effects: No systemic effects of Rabeprazole were found in the central nervous system, the cardiovascular system and the respiratory system. Rabeprazole in doses of 20 mg orally for 2 weeks, had no effects on thyroid function, metabolism of carbohydrates, or serum levels of parathyroid hormone, cortisol, estrogen, testosterone, prolactin, cholecystokinin, secretin, glucagon, follicle stimulating hormone (FSH), luteinizing hormone (LH), renin, aldosterone or somatotrophic hormone.

Studies in healthy individuals have shown that Rabeprazole does not have clinically significant interactions with amoxicillin or clarithromycin when administered together for the eradication of *H. pylori* from the upper gastrointestinal tract.

Pharmacokinetics

Absorption: Rabec[®] is a Rabeprazole sodium gastro-resistant coated tablet. This formulation is necessary because Rabeprazole is acid labile. Rabeprazole absorption begins after the tablet leaves the stomach. The absorption is rapid with a plasma peak at about 3.5 hours after a dose of 20 mg. The rabeprazole C_{max} and AUC (Area under the curve) have a linear behavior within a dose range of 10 to 40 mg. The absolute bioavailability of an oral dose of 20 mg (compared to intravenous administration) is approximately 52% due in large part to its presystemic metabolism. Bioavailability does not appear to increase with repeated administration. In healthy individuals the plasma half-life is of approximately 1 hour (range 0.7 to 1.5 hours.), and the clearance is about 283 ± 98 ml / min. Neither food nor time of day of administration has shown to affect the absorption of Rabeprazole sodium.

Distribution: Rabeprazole is 97% bound to plasma proteins.

Metabolism and Elimination: Rabeprazole is metabolized by cytochrome P450. In vitro studies using human liver microsomes indicated that Rabeprazole sodium is metabolized by CYP2C19 and CYP3A4 isozymes. It was found in these studies that rabeprazole does not induce or inhibit CYP3A4. While in vitro studies do not predict the in vivo response, these findings indicate that an interaction between Rabeprazole and cyclosporine is not to be expected. In humans, thioether (M1) and carboxylic acid (M6) are the main metabolites. Only the desmethyl metabolite (M3) has a mild antisecretory activity, but it is not found in plasma.

Following a single 20 mg dose of 14C-labeled Rabeprazole, there was no urinary excretion of unchanged drug. Approximately 90% of the dose was excreted in urine mainly as carboxylic acid (M6) and mercapturic acid (M5) metabolites, along with other metabolites. The rest of the dose is eliminated through feces.

Features in special patient groups

Gender: After adjusting for body mass index and height, there are no significant gender differences in pharmacokinetic parameters after a single dose of rabeprazole 20 mg.

Renal impairment: In patients with renal failure requiring dialysis (with

creatinine clearance ≤ 5 ml/min/1.73m2), the disposition of rabeprazole was similar to that found in healthy individuals. The AUC (Area under the curve) and C_{max} (maximum concentration) in these patients was 35% lower than in healthy volunteers. The half-life was 0.82 hours in healthy volunteers, 0.95 hours during hemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients requiring hemodialysis was approximately twice that found in healthy volunteers.

Hepatic impairment: Following administration of a single dose of 20 mg of Rabeprazole to patients with chronic mild to moderate hepatic impairment, the AUC and C_{max} doubled and half-life increased 2 to 3 times compared to healthy volunteers. However, after a daily dose of 20 mg for 7 days, the AUC increased 1.5 fold and C_{max} 1.2-fold. The half-life of Rabeprazole in patients with liver failure was 12.3 hours compared with 2.1 hours in healthy volunteers. Pharmacodynamics' response in both groups (Control of gastric pH) was clinically comparable.

Elderly: The elimination of Rabeprazole was diminished in this age group. After 7 days of administration of a daily dose of 20 mg of Rabeprazole sodium, the AUC was almost doubled, C_{max} increased by 60% and half-life increased approximately 30% compared to young healthy volunteers. But there was no evidence of accumulation of rabeprazole.

CYP2C19 polymorphism: After a daily dose of 20 mg for 7 days, poor metabolizers had an AUC and half-life 1.9 and 1.6 times respectively higher than the parameters for faster metabolizers, while the C_{max} increased only 40%.

DOSAGE AND ADMINISTRATION

Rabec[®] tablets should be swallowed whole. The tablets should not be chewed, or split.

Treatment of active duodenal ulcer and active benign gastric ulcer

The recommended dose for the treatment of both active duodenal ulcer and of active benign gastric ulcer is 20 mg once daily in the morning. Most active duodenal ulcer patients achieve resolution of symptoms within four weeks of treatment. However, some patients may require four weeks of treatment more to achieve healing. The majority of patients with active benign gastric ulcer resolve their symptoms within six weeks of treatment. However, some patients may also require an additional six weeks of treatment to achieve healing.

Treatment of erosive or ulcerative gastroesophageal reflux disease (GERD)

The recommended dose for this disease is 20 mg once daily for four to eight weeks.

Maintenance in Treatment of erosive or ulcerative GERD

For long-term management, a maintenance dose of Rabec[®] 20 mg or 10 mg once daily may be given taking into account the patient's response.

Treatment of symptomatic moderate to severe GERD

The recommended dose for patients without esophagitis is 10 mg once daily. In case of failure to achieve control of symptoms after 4 weeks of treatment, the patient should be studied. Once symptoms have cleared, a subsequent symptom control may be achieved using an on demand regimen of 10 mg once daily as needed.

Zollinger – Ellison syndrome

The recommended starting dose for adults is 60 mg once daily. The dose may be titrated, reaching up to 120 mg / day according to individual patient needs. A single daily dose of up to 100 mg / day may be administered. It may be necessary to separate daily doses of 120 mg in two doses of 60 mg. The treatment should be continued according to clinical indication.

Eradication of Helicobacter Pylori

Patients infected with *H. Pylori* should be treated with eradication therapy. We recommend the administration of the following combinations for 7 days. Rabec[®] 20 mg twice daily + clarithromycin 500 mg twice daily + amoxicillin 1g twice daily.

In the case of indications requiring a single daily dose, it must be administered before the meal. While neither the time of day it is ingested nor the combination with food has been shown to affect the activity of Rabeprazole, this regimen facilitates adherence to treatment.

Hepatic and renal impairment: No dosage adjustment is necessary in patients with renal or hepatic impairment. See warnings and precautions for use of Rabec[®] in patients with severe liver failure.

Pediatric use: The use of Rabec[®] in children is not recommended, since there is no experience with its use in this age group.

CONTRAINDICATIONS

Hipersensitivity to the active drug or to any component of the formulation. Severe hepatic failure. Pregnancy. Lactation.

WARNINGS

Because the symptomatic response to treatment with Rabeprazole does not rule out the presence of gastric or esophageal carcinoma, it is recommended to exclude the possibility of this diagnosis before starting treatment with Rabec[®].

PRECAUTIONS

Patients receiving long-term treatment (particularly those treated for more than a year) should be evaluated regularly by their doctor.

The risk of cross-hypersensitivity with other inhibitors of proton pump or benzimidazole derivatives can not be excluded.

The tablets should be swallowed whole without chewing or breaking them. Rabec[®] is not recommended for use in children since safety and efficacy in children has not been established.

There have been postmarketing Rabeprazole reports of blood dyscrasias (thrombocytopenia and neutropenia). In most cases in which an alternative etiology could not be identified, these events were not complicated and resolved on discontinuation of the use of Rabeprazole.

Changes in liver enzymes have been observed and have been reported in clinical studies. In most cases in which an alternative etiology could not be identified, these events were not complicated and resolved on discontinuation of the use of Rabeprazole.

No significant disorders were observed during treatment with Rabeprazole in patients with mild or moderate hepatic dysfunction in controlled studies. However, since there is no clinical data on the use of Rabeprazole in severe liver dysfunction, we recommend close medical supervision if used in patients with this disease.

Concomitant administration of atazanavir with Rabec[®] is not recommended.

Interactions

Since Rabeprazole inhibits gastric acid secretion, interaction may occur with drugs whose absorption depends on gastric pH. For example, coadministration of Rabeprazole with ketoconazole or itraconazole, or digoxin may reduce plasma levels of antifungals and increase levels of digoxin. For this reason, some patients may require dosage adjustment of these drugs.

In clinical studies, no interaction was observed with concomitant use of liquid antacids and Rabeprazole.

Coadministration of atazanavir 300 mg / ritonavir 10 mg and omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg / day) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, it is expected that similar results are obtained with other proton pump inhibitors. For this reason, inhibitors of proton pump, including Rabeprazole, should not be administered in conjunction with atazanavir.

Pregnancy and lactation

Pregnancy: Rabec[®] is contraindicated during pregnancy. There are no data on the safety of Rabeprazole in human pregnancy. Studies in rabbits and rats revealed no evidence of impaired fertility or harm to the fetus secondary to Rabeprazole.

Lactation: Rabec[®] is contraindicated during lactation. It is not known if rabeprazole is excreted in breast milk. There have been no studies in women during lactation. However rabeprazole is excreted in breast secretions of rats.
Pediatric use: The use of Rabec[®] in children is not recommended, since there is no experience with its use in this age group.

ADVERSE REACTIONS

The most frequently reported adverse reactions in clinical studies with rabeprazole include headache, diarrhea, abdominal pain, asthenia, flatulence, rash and dry mouth. Most adverse events were of mild to moderate severity and transient in nature.

The following adverse reactions have been reported during the marketing of rabeprazole and in clinical studies:

Frequencies are defined as: common (> 1 / 100, <1 / 10), uncommon (> 1 / 1000, <1 / 100), rare (> 1 / 10000, <1 / 1000) and very rare (<1 / 10000).

<i>Organ or system</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Very Rare</i>	<i>Unknown</i>
Infections and infestations	Infection				
Blood and lymphatic system			Neutropenia <p>Leukopenia</p> <p>Thrombocytopenia</p> <p>Leukocytosis</p>		
Immune System			Hipersensitivity ^{1,2}		
Metabolism and nutrition			Anorexia		Hyponatremia
Psychiatric disorders	Insomnia	Nervousness	Depression		Confusion
Nervous System	Headache <p>Dizziness</p>	Drowsiness			
Ophthalmologic disturbances			Visual disturbances		
Vascular disturbances					Peripheral Edema
Respiratory, thoracic and mediastinal disorders	Cough <p>Pharyngitis</p> <p>Rhinitis</p>	Bronchitis <p>Sinusitis</p>			
Gastrointestinal disorders	Diarrhea <p>Vomiting</p> <p>Nausea</p> <p>Abdominal pain</p> <p>Constipation</p> <p>Flatulence</p>	Dyspepsia <p>Dry mouth</p> <p>Belching</p>	Gastritis <p>Stomatitis</p> <p>Taste disturbance</p>		
Hepato-biliary disorders			Hepatitis <p>Jaundice</p> <p>Hepatic Encephalopathy ³</p>		
Skin and subcutaneous tissue disorders		Erythema <p>Rash</p>	Pruritus <p>Sweating</p> <p>Bullous reaction ²</p>	Erythema multiforme <p>Toxic epidermal necrosis</p> <p>Stevens Johnson Syndrome</p>	
Musculoskeletal, connective tissue and bone disorders	Nonspecific pain <p>LBP</p>	Myalgia <p>Lower limbs cramps</p> <p>Arthralgia</p>			
Renal and urinary disorders		Urinary infection	Interstitial nephritis		
Reproductive system and breast					Gynecomastia
General state	Asthenia <p>Influenza like illness</p>	Chest pain <p>Chills</p> <p>Pyrexia</p>			
Investigations		Increased liver enzymes	Weight gain		

1- Includes facial swelling, hypotension and dyspnea.

2- Erythema, bullous reaction and hypersensitivity reactions generally have resolved after discontinuation of treatment.

3- There have been rare reports of hepatic encephalopathy in patients with underlying cirrhosis. In the treatment of patients with severe liver failure, physicians should be careful at indicating the first start of treatment with Rabec[®].

Laboratorio
ELEA PHOENIX

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