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Rabeprazole

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Contents

Summary

▲ Rabeprazole is a proton pump inhibitor with antisecretory properties. *In vitro* animal experiments have indicated that the inhibition of the proton pump by rabeprazole is partially reversible.

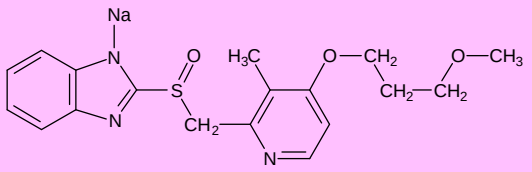
▲ Rabeprazole has 2- to 10-fold greater antisecretory activity than omeprazole *in vitro*. However, it dissociates more readily from H^+,K^+-ATPase than omeprazole, resulting in a shorter duration of action.

▲ In comparative clinical trials rabeprazole was significantly more effective than placebo, famotidine or ranitidine and as effective as omeprazole in the treatment of patients with erosive or ulcerative gastro-oesophageal reflux disease or gastric or duodenal ulcers. Healing rates with rabeprazole were independent of *Helicobacter pylori* status.

▲ Rabeprazole in combination with either clarithromycin and metronidazole or clarithromycin and amoxicillin or amoxicillin and metronidazole or clarithromycin for 7 days produced eradication of *H. pylori* in 100, 95, 90 and 63% of patients.

▲ The tolerability profile of rabeprazole 20mg once daily was similar to that of famotidine 20mg twice daily, ranitidine 150mg 4 times daily or omeprazole 20mg once daily in comparative trials. The adverse events reported with once daily administration of rabeprazole 20mg include malaise, nausea, diarrhoea, headache, dizziness and skin eruptions in 0.7 to 2.2% of patients.

Features and properties of rabeprazole (E 3810, LY 307640, pariprazole)	
Indications	
Duodenal ulcer Gastric ulcer Reflux oesophagitis *Helicobacter pylori* eradication	Launched (Japan) Late phase clinical trials
Mechanism of action	
Proton pump (H^+,K^+-ATPase) inhibitor	Antisecretory Gastroprotective
Dosage and administration	
Usual dosage in clinical trials	20 mg/day
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (20mg)	
Peak plasma concentration	0.406 mg/L
Time to peak plasma concentration	3.1h
Serum protein binding	96.3%
Area under the plasma concentration-time curve	0.809 mg/L • h
Clearance	35.3 L/h
Plasma half-life	1.02h



Rabeprazole (E 3810, LY 307640, pariprazole)

Acid peptic disease is characterised by epigastric pain, dyspepsia and occasionally nausea and vomiting and is often associated with *Helicobacter pylori* infection. Treatment is aimed at providing pain relief, promoting healing of mucosal lesions and preventing complications and recurrence by decreasing acid secretion, neutralising acid and eradicating *H. pylori*. The most commonly used antisecretory agents are the proton pump (H^+,K^+-ATPase) inhibitors and the H_2 receptor antagonists.

Rabeprazole is a benzimidazole proton pump inhibitor, the chemical structure of which differs from that of omeprazole due to substitutions on the pyridine and benzimidazole rings. It is a partially reversible inhibitor of H^+,K^+-ATPase and is activated in the acidic lumen of gastric parietal cells.

1. Pharmacodynamic Profile

Antisecretory Effects

- Rabeprazole was significantly more potent than omeprazole in inhibition of H^+,K^+-ATPase activity and acid output in animal models.[1-4] However, rabeprazole appears to dissociate more quickly and completely from H^+,K^+-ATPase than omeprazole, suggesting a reversible inhibition of the proton pump by rabeprazole.[4,5]

- In porcine gastric vesicles rabeprazole binds to H^+,K^+-ATPase at the Cys^{813}[6] or the Cys^{322}[7] residue located at the boundary between the lumen and the transmembrane domain in the E_1 form (proton binding site facing the cytosol), in contrast to omeprazole (E_2 form).[8] In addition to inhibition of ATP binding and phosphorylation (as seen with omeprazole), rabeprazole also inhibited K^+-dependent dephosphorylation of H^+,K^+-ATPase.[9]

- Rabeprazole showed a quick onset of action and almost complete inhibition of H^+,K^+-ATPase in porcine gastric vesicles took 5 minutes with rabeprazole and 30 minutes with omeprazole and lansoprazole.[6]

- In rats, acid secretion and the H^+,K^+-ATPase activity recovered more quickly than after a similar dose of lansoprazole.[10] Incubation with dithiothreitol reversed rabeprazole inhibition of H^+,K^+-ATPase in isolated microsomes from these animals, but did not reverse lansoprazole-mediated inhibition.[11,12]

- Single oral doses of rabeprazole 10, 20, 30 or 40mg (n = 10 volunteers per group) produced dose-dependent increases in both the extent and duration of acid inhibition.[13]

- In several well designed studies in volunteers, rabeprazole 5 to 40 mg/day for 7 to 14 days caused significant decreases in gastric acidity and significant increases in plasma gastrin levels versus placebo.[14-16] Rabeprazole 20 mg/day resulted in significantly greater plasma gastrin levels than omeprazole 20 mg/day and had a significantly quicker onset of action.[17]

- In patients with gastro-oesophageal reflux disease, rabeprazole 20 mg/day for 8 weeks caused significantly greater increases in serum gastrin levels than ranitidine 600 mg/day.[18] Rabeprazole 20 and 40 mg/day significantly decreased oesophageal acid exposure and daily reflux episodes in a similar group of patients.[19]

- In patients (number not stated) with peptic ulcer the percentage of total time that intragastric pH was >3 increased from 35.5% before treatment to 99.4%, 83.7%, and 65.1% during treatment with rabeprazole 20 mg/day, omeprazole 20 mg/day or famotidine 40 mg/day, respectively. After stopping treatment, the effect of rabeprazole disappeared within 2 days, while the inhibitory effect of omeprazole persisted for at least 4 days.[20]

Other Effects

- Rabeprazole 20 mg/kg/day administered by gavage to rats for 2 weeks increased intracellular mucin content and new mucin synthesis in gastric mucosa. Omeprazole decreased mucin content and new mucin synthesis, whereas lansoprazole had no effect.[21]

- Rabeprazole or omeprazole 20 mg/kg reduced gastric lesions and prevented increases in mucosal leukotrienes C_4 and D_4 caused by water immersion stress in rats. Neither agent, however, affected the decrease in mucosal prostaglandin content.[22]

- In a model of gastric lesions in the rat, unlike H_2 receptor antagonists, rabeprazole did not suppress collagen regeneration or delay healing of gastric lesions.[23]

- Rabeprazole 20 mg/day or placebo for 14 days did not alter any endocrine function (including serum levels of testosterone, dehydroepiandrosterone, circadian cortisol, cortisol binding globulin, insulin, glucagon, renin, aldosterone, estrogen and thyroid function tests) from pretreatment levels in 12 healthy volunteers in a randomised, double-blind, crossover trial (washout period between treatments not stated).[24]

Antibacterial Activity Against *H. pylori*

- Rabeprazole showed greater *in vitro* antimicrobial activity against *H. pylori* than omeprazole and lansoprazole.[25] Rabeprazole was reported to attach directly at several sites on *H. pylori*,[26] and the bacterial urease enzyme is irreversibly and noncompetitively inhibited by rabeprazole.[27]

- The combination of rabeprazole and amoxicillin did not display any *in vitro* synergism against *H. pylori*, but combination of amoxicillin and the thioether metabolite of rabeprazole resulted in reduced minimum inhibitory concentrations (MICs) compared with the individual compounds alone.[28]

- In a clinical study in 26 volunteers positive for *H. pylori* using the ^{13}C-urea breath test, rabeprazole 20 and 40 mg/day (duration not stated) were similar to placebo in eradicating *H. pylori*. In a second part of the study in 48 volunteers, combination of rabeprazole 40 mg/day with amoxicillin 2 g/day produced a greater eradication rate than amoxicillin 2 g/day alone (63 *vs* 13%).[29]

- The combination of rabeprazole 20mg twice daily with twice daily doses of either clarithromycin 500mg and metronidazole 400mg (n = 18) or amoxicillin 1g and clarithromycin 500mg (n = 19) or amoxicillin 1g and metronidazole 400mg (n = 19) or clarithromycin 500mg (n = 19) for 7 days was associated with *H. pylori* eradication in 100, 95, 90 and 63% of patients in each group.[30] The eradication rates in the first 2 groups were statistically superior to those observed in the group receiving rabeprazole plus clarithromycin.

2. Pharmacokinetic Profile

- After single oral doses of rabeprazole 10 to 80mg in 18 Japanese volunteers, the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values were dose dependent, but time to C_{max} (t_{max}), plasma half-life ($t_{½}$) and clearance (CL) were not. After a 20mg dose C_{max} was 0.406 mg/L, t_{max} was 3.1 hours, AUC was 0.809 mg/L · h, $t_{½}$ was 1.02 hours and CL was 0.504 L/h · kg (or 35.3 L/h in a 70kg individual).[31]

- Plasma protein binding of rabeprazole ranged from 94.8 to 97.5% in healthy volunteers. Although C_{max} values did not change with the presence of food, t_{max} was significantly prolonged (by 1.7 hours) after meals.[31]

- After once-daily administration of rabeprazole 40mg for 7 days, C_{max} was 0.418 mg/L, t_{max} was 3.8 hours, AUC was 1.036 mg/L · h, $t_{½}$ was 1.49 hours and CL was 0.648 L/h · kg. The total cumulative urinary excretion over 48 hours of the rabeprazole thioether carboxylic acid metabolite plus its glucuronide accounted for approximately 34% of the total dose given.[31]

- No substantial change occurred in drug pharmacokinetics during repeated daily oral administration of rabeprazole 20 or 40mg. The t_{max} after the last dose was significantly shorter than after the first dose in the 40 mg/day group (probably because of partial dissolution of the enteric-coated

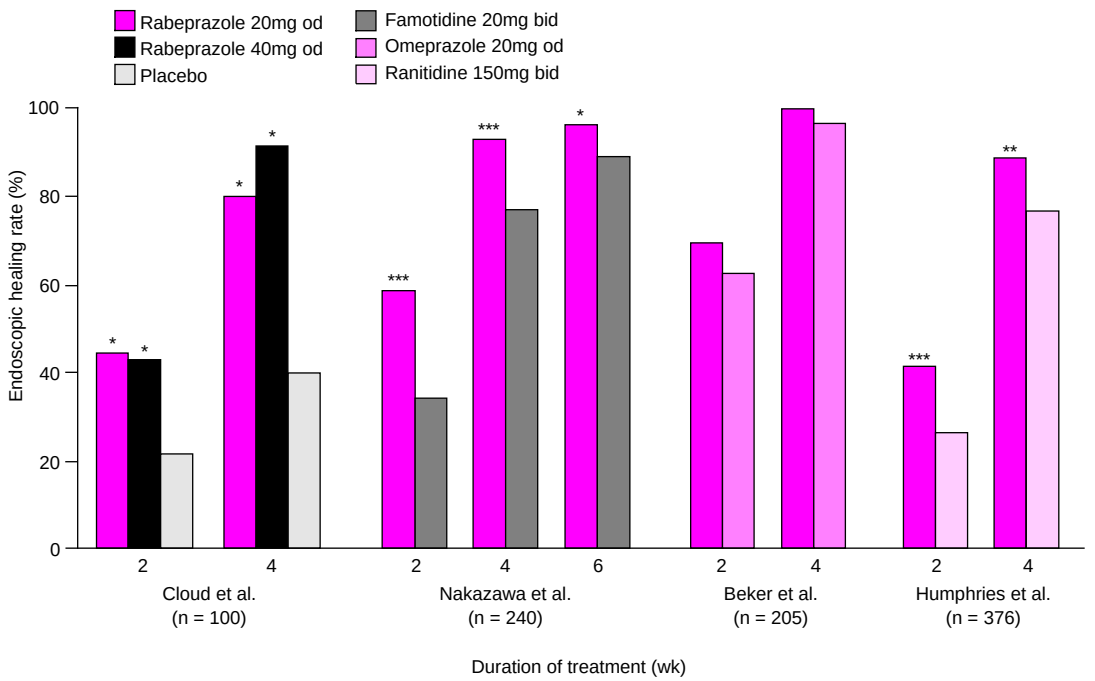


Fig. 1. Efficacy of rabeprazole compared with placebo (Cloud et al.[39]), famotidine (Nakazawa et al.[40]), omeprazole (Beker et al.[41]) or ranitidine (Humphries et al.[42]) in the treatment of duodenal ulcers. Results of multicentre, double-blind trials. *Abbreviations and symbols:* bid = twice daily; od = once daily; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ *vs* comparator.

tablet due to raised gastric pH) and $t_{1/2}$ tended to increase.[31]

• In a 7-day randomised, crossover trial, CL of rabeprazole or omeprazole 20 mg/day was significantly lower and mean AUC was significantly greater in poor metabolisers of S-mephenytoin (n = 6) than in extensive metabolisers (n = 9), although the difference between values was smaller during rabeprazole administration.[32]

• Studies in healthy human volunteers did not reveal any drug interaction between rabeprazole and diazepam,[33] theophylline, warfarin,[34] or phenytoin.[35] Coadministration of rabeprazole decreased AUC and C_{max} of ketoconazole, while ketoconazole had no effect on rabeprazole metabolism.[36] It is recommended that rabeprazole should be discontinued before starting therapy with ketoconazole.[37] Administration of rabeprazole 20 mg/day to volunteers receiving digoxin 0.25 mg/day has been found to increase AUC, C_{max} and $t_{1/2}$ of digoxin. The authors suggested monitoring of digoxin concentrations in patients receiving digoxin and rabeprazole.[38]

3. Therapeutic Trials

All clinical studies of rabeprazole evaluated the oral formulation. In studies assessing this agent for the treatment of gastric and duodenal ulcers and gastro-oesophageal reflux disease, the primary parameter for efficacy was mucosal healing, which was documented endoscopically.

Duodenal Ulcers

• In 100 patients with duodenal ulcers (fig. 1), rabeprazole 20 and 40 mg/day produced similar healing rates at 4 weeks (79.4 and 90.9%), which were superior ($p < 0.05$) to those in the placebo group (39.4%).[39]

• Over 6 weeks, rabeprazole 20mg once daily showed significantly greater efficacy than famotidine 20mg twice daily in 240 patients with duodenal ulcers (fig. 1): the cumulative healing rates in the rabeprazole and famotidine groups were 58.0 *vs* 33.7% at 2 weeks, 92.3 *vs* 76.5% at 4 weeks, and 95.5 *vs* 88.5% at 6 weeks.[40]

• In 2 large studies (fig. 1) rabeprazole 20 mg/day produced healing rates similar to omeprazole 20 mg/day in 205 patients (99 *vs* 96% at 4 weeks)[41] and superior to ranitidine 300 mg/day in 376 patients (88 *vs* 76% at 4 weeks).[42] Rabeprazole was associated with a significantly greater improvement in daytime pain severity at week 4 compared with omeprazole,[41] and night-time pain and complete pain resolution at week 2 compared with ranitidine (pain assessment methods not stated).[42]

Gastric Ulcers

• In a US study in 94 patients with gastric ulcers rabeprazole 20 and 40 mg/day produced similar healing rates at 6 weeks that were superior ($p \leq 0.003$) to those in placebo recipients (93, 96 and 55%, respectively) (fig. 2). The frequency and severity of ulcer pain were also improved compared with placebo recipients.[43]

• In a Japanese study comparing the efficacy of rabeprazole 20mg once daily with famotidine 20mg twice daily in 241 patients with gastric ulcers (fig. 2), the cumulative healing rates in the rabeprazole-treated group were superior to those in the famotidine-treated group at all time points (19.1 *vs* 5.9% at 2 weeks, 73.0 *vs* 30.1% at 4 weeks, 94.1 *vs* 64.6% at 6 weeks, and 97.2 *vs* 78.4% at 8 weeks.[44]

Gastro-Oesophageal Reflux Disease

• The effects of rabeprazole 20mg once daily were significantly superior to those of ranitidine 150mg 4 times daily, at all time points, in 338 patients with erosive or ulcerative gastro-oesophageal reflux disease (fig. 3). Heartburn resolved more completely in the rabeprazole-treated patients ($p < 0.001$).[18]

• The endoscopic healing rates with rabeprazole and omeprazole 20 mg/day were comparable at 4 and 8 weeks in 202 patients (fig. 3).[45]

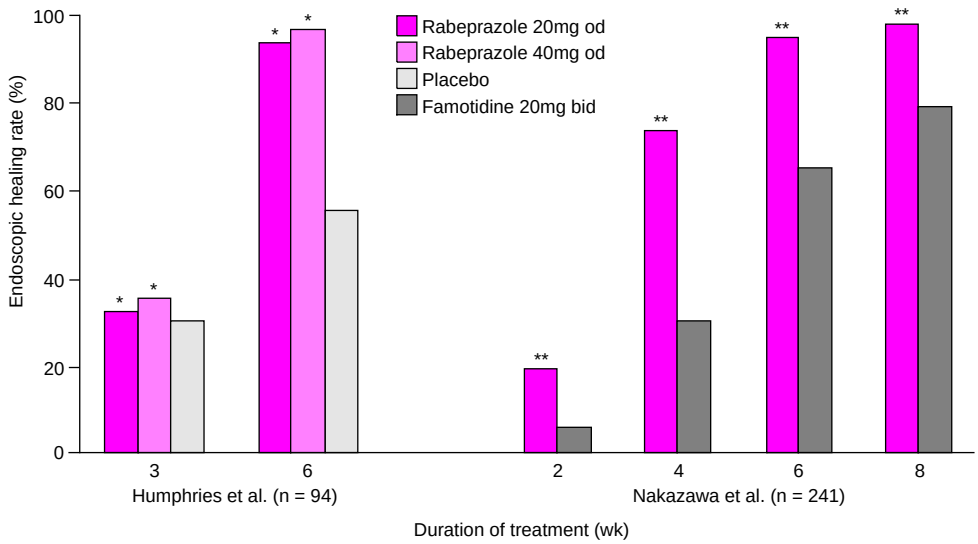


Fig. 2. Efficacy of rabeprazole compared with placebo (Humphries et al.[43]) or famotidine (Nakazawa et al.[44]) in the treatment of gastric ulcers. Results of multicentre, double-blind trials. *Abbreviations and symbols:* bid = twice daily; od = once daily; * $p \leq 0.05$; ** $p \leq 0.001$ *vs* comparator.

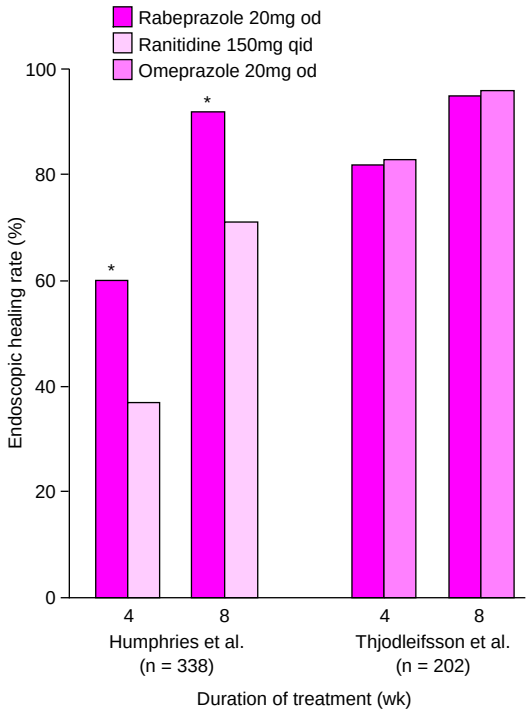


Fig. 3. Efficacy of rabeprazole compared with ranitidine (Humphries et al.[18]) and omeprazole (Thjodleifsson et al.[45]) in treating erosive/ulcerative gastro-oesophageal reflux disease. Results of multicentre, double-blind, parallel studies. *Abbreviations and symbol:* od = once daily; qid = 4 times daily; * $p \leq 0.001$ *vs* comparator.

4. Tolerability

• In the comparative trials reviewed in section 3, rabeprazole 20 and 40 mg/day were similarly or better tolerated than famotidine 40 mg/day,[40,44] ranitidine 300 mg/day[42] or 600 mg/day,[18] omeprazole 20 mg/day[41,45] or placebo over 4 to 8 weeks. In 2 large studies, adverse events were reported in 1 of 140[44] and 3 of 137[40] patients treated with rabeprazole 20 mg/day for 8 and 6 weeks, respectively. Adverse events with rabeprazole were mild to moderate in intensity and included malaise, diarrhoea, nausea, skin eruptions, headache and dizziness. Abnormal laboratory findings (increased hepatic enzymes, platelet count, total cholesterol, lactate dehydrogenase, white blood cell count or blood urea nitrogen) observed with rabeprazole were similar in incidence and severity to those observed with comparator agents and reversible on cessation of therapy.

5. Rabeprazole: Current Status

Rabeprazole is a proton pump inhibitor that has been launched in Japan and is in late phase clinical trials elsewhere. It has shown clinical efficacy in the management of duodenal and gastric ulcers and gastro-oesophageal reflux disease. The tolerability profile of rabeprazole is similar to that of other antisecretory agents.

References

1. Morii M, Takata H, Fujisaki H, et al. The potency of substituted benzimidazoles such as E3810, omeprazole, Ro-18-5364 to inhibit gastric H^+,K^+-ATPase is correlated with the rate of acid-activation of the inhibitor. Biochem Pharmacol 1990 Feb 15; 39: 661-7
2. Fujisaki H, Murakami M, Fujimoto M, et al. The activity of isolated porcine H^+,K^+-ATPase is inhibited by E3810 (2-[{4-(3 - methoxypropoxy) - 3 - methylpyridin - 2 - yl} - methylsulfinyl] -1H- benzi midazole, sodium) [abstract]. FASEB J 1990 Feb 26; 4: 473
3. Oketani K, Murakami M, Fujimoto M, et al. The secretion of acid from isolated rabbit gastric glands is inhibited by E3810 (2 - [{4 - (3 - methoxypropoxy) - 3 - methylpyridin - 2 - yl} - methylsulfinyl]-1H-benzimidazole, sodium) [abstract]. FASEB J 1990 Feb 26; 4: 473
4. Shibata H, Murakami M, Fujimoto M, et al. Histamine-stimulated gastric acid secretion is inhibited in gastric fistula dogs treated with E3810 (2-[{4-(3-methoxypropoxy)-3-methylpyridin-2-yl}-methylsulfinyl]-1H-benzimidazole, sodium) [abstract]. FASEB J 1990 Feb 26; 4: 473
5. Fujisaki H, Shibata H, Oketani K, et al. Inhibitions of acid secretion by E3810 and omeprazole, and their reversal by glutathione. Biochem Pharmacol 1991 Jul 5; 42: 321-8
6. Besancon M, Simon A, Sachs G, et al. Sites of reaction of the gastric H^+,K^+-ATPase with extracytoplasmic thiol reagents. J Biol Chem 1997; 272: 22438-46
7. Morii M, Hamatani K, Takeguchi N. The proton pump inhibitor, E3810, binds to the N-terminal half of the alpha-subunit of gastric H^+,K^+-ATPase. Biochem Pharmacol 1995 Jun 16; 49: 1729-34
8. Morii M, Takeguchi N. The conformational state of proton pump is differently affected by omeprazole, lansoprazole and E3810 [abstract no. 1994P]. 10th World Congress on Gastroenterology 1994
9. Morii M, Takeguchi N. Different biochemical modes of action of two irreversible H^+,K^+-ATPase inhibitors, omeprazole and E3810. J Biol Chem 1993 Oct 15; 268: 21553-9
10. Takeguchi N, Tomiyama Y, Morii M. The intracellular cycling of gastric proton pump is differently affected by E3810 and lansoprazole [abstract no. 1996P]. 10th World Congress on Gastroenterology 1994
11. Takeguchi N, Tomiyama Y, Morii M. E3810 and lansoprazole differently affect the proton pump cycling [abstract]. Z Gastroenterol 1993 Sep; 31: 579
12. Tomiyama Y, Morii M, Takeguchi N. Specific proton pump inhibitors E3810 and lansoprazole affect the recovery process

of gastric secretion in rats differently. Biochem Pharmacol 1994 Nov 29; 48: 2049-55
13. Rogers SL, Sytnik B, Kovacs T, et al. A study of the pharmacodynamics of E3810, a new and partially reversible inhibitor of H^+,K^+-ATPase in healthy male volunteers [abstract]. Gastroenterology 1993 Apr; 104 Suppl.: A180
14. Blanshard C, Millson C, Sercombe J, et al. The effects of rabeprazole on 24-hour intragastric acidity and plasma gastrin concentration in healthy subjects [abstract]. Gut 1996; 39 Suppl. 3: 47-8
15. Kovacs TOG, Sytnik B, Humphries TJ, et al. A low dose of a new proton pump inhibitor LY-307640 (E3810) effectively inhibits acid secretion in humans [abstract]. Gastroenterology 1996 Apr; 110 Suppl.: 161
16. Dammann HG, Burkhardt F, Bell NE, et al. Rabeprazole effectively inhibits 24 hr H^+ activity and nocturnal acid secretion in healthy subjects [abstract]. Gut 1996; 39 Suppl. 3: 47
17. Williams M, Sercombe J, Pounder RE. Comparison of the effects of rabeprazole and omeprazole on 24-hour intragastric acidity and plasma gastrin concentration in healthy subjects [abstract]. Am J Gastroenterol 1997; 92 (9): 1627
18. Humphries TJ, Spera A, Breiter J. Rabeprazole sodium (E3810) once daily is superior to ranitidine 150 mg QID in the healing of erosive or ulcerative gastroesophageal reflux disease [abstract]. Gastroenterology 1996 Apr; 110 Suppl.: 139
19. Robinson M, Maton PN, Rodriguez S, et al. Effects of oral rabeprazole on oesophageal and gastric pH in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1997; 11: 973-80
20. Inoue M, Shirakawa T, Murakami Y, et al. Effect of a new proton pump inhibitor E3810 on intragastric pH in the patients with peptic ulcer [abstract]. Gastroenterology 1991 May; 100 Suppl.: 89
21. Takiuchi H, Asada S, Umegaki E, et al. Effects of proton pump inhibitors, omeprazole, lansoprazole and E-3810, on the gastric mucin [abstract no. 1404P]. 10th World Congress on Gastroenterology 1994
22. Goto H, Sugiyama S, Tsukamoto Y, et al. Effects of two benzimidazoles as proton pump inhibitors on water immersion stress-induced gastric ulcers in rats. Arzneimittel Forschung 1991 Jun; 41: 635-7
23. Suzuki T, Tsukamoto Y, Goto H, et al. Effects of histamine-H(2)-receptor antagonists and a proton pump inhibitor on the mucosal hydroxyproline content of ethanol-HCl-induced gastric lesions in rats. Digestion 1992 Mar; 51: 161-7
24. Dammann HG, Burkhardt F. Rabeprazole does not affect endocrine function in healthy subjects [abstract]. Am J Gastroenterol 1996 Sep; 91: 1909
25. Satoh M, Tonomura H, Murakami M, et al. In vitro activity of E3810/LY307640, a novel proton pump inhibitor, against *Helicobacter pylori* [abstract no. 196P]. 10th World Congress on Gastroenterology 1994
26. Hirai M, Azuma T, Ito S, et al. A proton pump inhibitor, E3810, has antibacterial activity through binding to *Helicobacter pylori*. J Gastroenterol 1995; 30 (4): 461-4
27. Park JB, Imamura L, Kobashi K. Kinetic studies of *Helicobacter pylori* urease inhibition by a novel proton pump inhibitor, rabeprazole. Biol Pharm Bull 1996 Feb; 19: 182-7
28. Moore R, Bryan LE, Satoh M, et al. Anti-*Helicobacter pylori* activity synergy between amoxicillin and the thioether derivative of the proton pump inhibitor E3810/LY307640 [abstract no. 197P]. 10th World Congress on Gastroenterology 1994
29. Humphries TJ, Bassion S, Spanyers SA. Pilot studies on the effects of rabeprazole sodium (E3810), amoxicillin, and placebo on the eradication of *H. pylori* [abstract]. Am J Gastroenterol 1996 Sep; 91: 1914
30. Stack W, Atherton J, Sen AK, et al. Rabeprazole is effective when used in combination with antibiotics for the eradication of *Helicobacter pylori* [abstract]. Am J Gastroenterol 1997; 92 (9): 1626
31. Yasuda S, Ohnishi A, Ogawa T, et al. Pharmacokinetic properties of E3810, a new proton pump inhibitor, in healthy male volunteers. Int J Clin Pharmacol Ther 1994 Sep; 32: 466-73
32. Yasuda S, Horai Y, Tomono Y, et al. Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4′-hydroxylation status. Clin Pharmacol Ther 1995 Aug; 58: 143-54
33. Ishizaki T, Chiba K, Manabe K, et al. Comparison of the interaction potential of a new proton pump inhibitor, E3810, versus omeprazole with diazepam in extensive and poor metabolizers of S-mephenytoin 4′-hydroxylation. Clin Pharmacol Ther 1995 Aug; 58: 155-64
34. Humphries TJ, Nardi RV, Spera AC, et al. Coadministration of rabeprazole sodium (E3810) does not effect the pharmacokinetics of anhydrous theophylline or warfarin [abstract]. Gastroenterology 1996 Apr; 110 Suppl.: 138
35. Humphries TJ, Spera AC, Laurent AL. Rabeprazole sodium (E3810) 20 mg daily does not affect the pharmacokinetics of phenytoin sodium in normal volunteers [abstract]. Am J Gastroenterol 1996 Sep; 91: 1914
36. Humphries TJ, Nardi RV, Spera AC, et al. Coadministration of rabeprazole sodium (E3810) and ketoconazole results in a predictable interaction with ketoconazole [abstract]. Gastroenterology 1996 Apr; 110 Suppl.: 138
37. Humphries TJ, Nardi RV, Lazar JD, et al. Drug-drug interaction evaluation of rabeprazole sodium: a clean/expected slate? [abstract]. Gut 1996; 39 Suppl. 3: 47
38. Humphries TJ, Spera AC, Laurent AL. Coadministration of rabeprazole sodium (E3810) and digoxin results in a predictable interaction [abstract]. Am J Gastroenterol 1996 Sep; 91: 1914
39. Cloud ML, Olovich K, Enas N. LY307640 versus placebo in healing duodenal ulcers [abstract]. Gastroenterology 1995 Apr; 108 Suppl.: A73
40. Nakazawa S, Namiki M, Matsuo Y, et al. Clinical utility of E3810 for the treatment of duodenal ulcer: comparison with famotidine by multi-center double-blind study [in Japanese]. Rinsho Hyoka 1993 Dec; 21: 361-82
41. Beker JA, Dekkers CPM, Thjodleifsson B, et al. Rabeprazole sodium 20mg once daily is similar to omeprazole 20mg once daily in the healing of active duodenal ulcer [abstract]. Gastroenterology 1997 May; 112 (4): A70
42. Humphries TJ, Spera A, Breiter J, et al. Rabeprazole sodium once daily is superior to ranitidine 150mg bid in the healing of active duodenal ulcer [abstract]. Gastroenterology 1997 May; 112 (4): A154
43. Humphries TJ, Cloud ML, Enas N, et al. Rabeprazole (E3810, LY307640) achieves high rates of healing in active gastric ulcer [abstract]. Gastroenterology 1996 Apr; 110 Suppl.: 138
44. Nakazawa S, Namiki M, Matsuo Y, et al. Clinical utility of E3810 for the treatment of gastric ulcer: comparison with famotidine by multi-center double-blind study [in Japanese]. Rinsho Hyoka 1993 Dec; 21: 337-59
45. Thjodleifsson B, Dekkers CPM, Beker JA, et al. Rabeprazole sodium 20mg once daily is similar to omeprazole 20mg once daily in the treatment of erosive or ulcerative GERD [abstract]. Gastroenterology 1997 May; 112 (4): A312

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