Pharmacy Benefits Management Strategic Healthcare Group

Medical Advisory Panel

Abbreviated Drug Class Review: Proton Pump Inhibitors

Written by Francine Goodman, Pharm.D., BCPS

The following class review is based on current literature and expert opinion from clinicians. It is expected that significant, new information will be forthcoming in this drug class. Thus, the following recommendations are dynamic and will be revised as new clinical data becomes available. This review is not intended to interfere with clinical judgment. Rather, it is intended to assist practitioners in providing cost effective, consistent, high quality care.

Objective

1. To provide an abbreviated review of the currently available proton pump inhibitors (PPIs) in the treatment of acid-related gastrointestinal disorders (see Table 1).

Table 1 Proton pump inhibitors available in the U.S.

Generic Name	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Brand Name	Nexium	Prevacid	Prilosec	Protonix	Aciphex
Manufacturer	AstraZeneca	TAP Pharm	Astra	Wyeth-Ayerst	Eisai/Janssen
Dosage forms	Caps, DR: 20, 40 mg	Caps, DR: 15, 30 mg Susp, DR (30 ml): 15, 30 mg	Caps, DR: 10, 20, 40 mg	Tabs, DR: 40 mg I.v. injection: 40 mg/vial	Tabs, DR: 20 mg

Caps = Capsules; DR = Delayed-release; I.v. = Intravenous; Susp = Suspension; Tabs = Tablets

2. To provide a brief comparison of the PPIs to aid in negotiating contracts for these agents for the Veterans Health Administration.

Indications and Dosage

The PPIs are FDA-approved for a variety of gastrointestinal acid-related disorders (see Table 2). Lansoprazole and omeprazole have the greatest number of approved indications for management of duodenal ulcers, gastric ulcers, GERD, or pathologic hypersecretory conditions.

Lansoprazole is the only PPI approved for healing or risk reduction of nonsteroidal anti-inflammatory drug (NSAID)-related gastric ulcers, and there is off-label experience with pantoprazole for this indication.[1] Healing and maintenance of erosive esophagitis are currently the main approved indications for pantoprazole, which is the first PPI available in a parenteral (intravenous) formulation for the short-term (7- to 10-day) treatment of GERD in patients who are unable to continue taking the oral tablets. Off-label use of pantoprazole in the management of duodenal and gastric ulcers has been documented in a number of double-blind randomized controlled trials (DBRCTs).[2-9] All of the PPIs have approved indications for treatment of erosive or ulcerative reflux esophagitis. Omeprazole has dosing recommendations specifically for treatment of non-erosive reflux disease.

Table 2 FDA-approved indications, off-label uses (OLUs), and dosages for PPIs

Indication	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Duodenal ulcers					
Healing	—	15 mg q.d. × 4 wk	20 mg q.d. × 4 to 8 wk	40 mg q.d. × 2 to 4 wk (OLU)	20 mg q.d. × ≤ 4 wk
Maintain healing	—	15 mg q.d.	10 to 20 mg q.d. (OLU)	—	—
Eradicate *Helicobacter pylori* associated with duodenal ulcers	40 mg q.d. × 10 d in 3-drug regimen	30 mg b.i.d. × 10 or 14 d in 2- or 3-drug regimens	20 mg b.i.d. or 40 mg q.d. × 28 d in various 2- or 3-drug regimens	—	20 mg b.i.d. × 5 to 7 d in various 2-, 3-, or 4-drug regimens (OLU-N)
Gastric ulcers					
Healing, non-NSAID–related	—	30 mg q.d. × ≤ 8 wk	40 mg q.d. × 4 to 8 wk	40 mg q.d. × 4 or 8 wk (OLU)	20 mg q.d. × 3 or 6 wk (OLU)
Healing, NSAID-related	—	30 mg q.d. × 8 wk	—	40 mg q.d. × 12 wk (OLU)	—
Reduce risk, NSAID-related	—	15 mg q.d. × ≤ 12 wk	—	40 mg q.d. × 12 wk (OLU)	—
GERD					
Relieve symptoms	20 mg q.d. × 4 wk	15 mg q.d. × ≤ 8 wk	(NERD) 20 mg q.d. × 4 wk	40 mg q.d. × 4 or 8 wk (OLU)	20 mg q.d. × 4 to 8 wk (OLU, including NERD)
Healing of erosive or ulcerative esophagitis	20 or 40 mg q.d. × 4 to 8 wk	30 mg q.d. × ≤ 8 wk	20 mg q.d. × 4 to 8 wk	40 mg q.d. × ≤ 8 wk	20 mg q.d. × 4 to 8 wk
Maintain healing of erosive or ulcerative esophagitis	20 mg q.d.	15 mg q.d.	20 mg q.d.	40 mg q.d.	20 mg q.d.
Short-term treatment of GERD as an alternative to oral therapy in patients unable to continue taking tablets	—	—	—	40 mg q.d. × 7 to 10 d (i.v.)	—
Posterior laryngitis, suspected GERD-related with or without esophageal symptoms	—	—	20 or 40 mg q.h.s. × 6 to 24 wk or 20 mg b.i.d. × 4 to 12 wk (OLU)	—	—
Hypersecretory conditions	—	60 to 180 mg a day in 1 or 2 divided doses	60 to 360 mg a day in 1 to 3 divided doses	—	60 or 120 mg a day in 1 or 2 divided doses

Sources: [1-35]

All doses refer to oral administration except as indicated.

OLU = Off-label use supported by at least one double-blind, randomized controlled trial comparing PPI to placebo or active comparator or rated as having at least "fair" documentation in *Off-Label Drug Facts* (2001).[16]

OLU-N = Off-label use supported by at least one noncomparative, double-blind, randomized trial or at least one comparative open-label randomized trial (where comparative refers to comparisons between rabeprazole and another PPI or placebo).

NERD = Non-erosive (endoscopy-negative) reflux disease

Dosing in special patient populations

Dosage adjustment of the PPIs may be necessary in patients with hepatic impairment (Table 3). None of the PPIs require dosage adjustment in renal impaired or elderly patients. Race-related pharmacokinetic differences have been noted in Asian patients treated with lansoprazole, omeprazole, and rabeprazole.

Table 3 Dosage adjustments in special populations

Population characteristic	Esomeprazole magnesium	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Hepatic impairment	Max. ≤ 20 mg q.d.	Severe impairment: decrease dose	Consider decrease in dose	Weigh risks vs. benefits of q.o.d. dosing	Severe impairment: use caution
Renal impairment	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Elderly	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Gender	No adjustment	No adjustment	No data	No adjustment	No adjustment
Race	No data	Limited data suggests increased AUC in Asians; no dosing recommendations	Consider decreasing dose in Asians	No data	AUC increased 50% to 60% in Japanese using different formulations; no dosing recommendations

Sources: [11-15]

Compliance factors

Alternative dosing packages or methods of administration that may improve patient convenience or aid patient adherence to medication regimens are available for all of the PPIs except rabeprazole (Table 4). According to the manufacturer (Eisai Inc. product information, verbal communication, June 2001), there are currently no alternative methods of administration for rabeprazole (which is available only as delayed-release tablets that must be swallowed whole) in patients who have difficulty swallowing or are unable to take oral medication.

Table 4 Alternative methods of administration

Indication / Problem	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole
H. pylori eradication	—	Prevpac® (lansoprazole / amoxicillin / clarithromycin) dosing package	—	—
Difficulty swallowing	Open capsule and sprinkle pellets in applesauce, tap water, orange juice, apple juice, or yogurt.	1. Delayed-release oral suspension 2. Open capsule and sprinkle granules in applesauce, *Ensure* pudding, cottage cheese, yogurt, strained pears, orange juice, or tomato juice. 3. Nasogastric (NG) administration: open capsules, mix intact granules with 40 ml of apple juice, then inject into NG tube.	1. Open capsule and sprinkle granules in applesauce or orange juice (OLU).[36] 2. Extemporaneously compounded omeprazole suspension (OLU).[37]	—
Unable to continue oral tablets	—	—	—	Intravenous formulation

OLU = Off-label use

Safety

Common adverse events

All of the available PPIs have been well tolerated in short- and long-term clinical trials with no remarkable differences in the adverse event profiles between agents. The most frequently reported adverse events (those occurring in greater than or equal to 1% of patients in at least one treatment group) affected the gastrointestinal or central nervous system (Table 5). Dose-related increases in the frequency of diarrhea were noted in premarketing clinical trials for lansoprazole. For the other PPIs, dose-related adverse events were either not observed (pantoprazole, rabeprazole) or not reported (esomeprazole, omeprazole).

Table 5 Most frequently occurring adverse events (≥ 1% of patients in at least one treatment group)

	Frequency as percentage (%) of patients [Rates in brackets refer to adverse events considered by the investigator to have possible, probable, or definite relationship to drug.]				
Adverse Event	**Esomeprazole**	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
Gastrointestinal System					
Diarrhea	4.3	— [1.4 to 7.4]	3.0 [1.9]	— [4 to 6]	NS
Abdominal pain	3.8	— [1.8]	2.4 [0.4]	— [1 to 4]	NS
Nausea	NS	— [1.4]	2.2 [0.9]	NS	NS
Central Nervous System					
Headache	3.8 to 5.5	— [> 1%]	3.8 to 6.9 [NS to 2.4]	— [6 to 9]	— [2.4]

Sources: [11-15]

Rates reflect the results of different clinical trials and are therefore not directly comparative.

NS = Not stated.

Studies in rats have found PPI-induced hyperplasia of gastric enterochromaffin-like (ECL) cells and, in some cases, gastric neuroendocrine cell tumors, which may result from chronic hypergastrinemia.[11-15] Time- and dose-related increases in the frequency of ECL cell hyperplasia and hypergastrinemia have been observed in patients treated with PPIs for 6 months to 5 years in clinical trials.[11-15] No dysplastic or neoplastic changes of the ECL cells in the gastric mucosa have been detected and no patient has developed the carcinoid tumors observed in rats.

Postmarketing Adverse Events

Voluntarily reported adverse events associated with postmarketing experience with the PPIs have been disclosed in the package inserts for lansoprazole, omeprazole, pantoprazole, and rabeprazole.[12-15] No data was available for esomeprazole, which was only recently marketed. Postmarketing adverse events have generally been consistent with short-term use of the PPIs and no clear differences between agents have been noted. Blood dyscrasias and serious allergic reactions have been reported. In many cases, a relationship with the PPI could not be established.

Drug Interactions

The two main mechanisms of drug-drug interactions relevant to PPIs are (1) inhibition or induction of CYP450 isoenzymes, and (2) alteration of drug absorption. These interactions are summarized in Table 6.

All of the available PPIs are metabolized by CYPs 2C19 and 3A4 to varying degrees. Other isoenzymes (1A2, 2C9, and 2D6) may be affected by the PPIs but are not involved in their metabolism.[38] Omeprazole has differential affinity for selected P450 isoenzymes.[39] Pantoprazole has a lower affinity for P450 and is also metabolized by a non-P450 enzyme, sulphotransferase.[38] Similarly, rabeprazole has lower affinity for 2C19 than omeprazole.[40]

Omeprazole has the greatest potential to cause drug interactions, while lansoprazole, pantoprazole and rabeprazole are less likely to be involved in CYP450-mediated drug interactions.[41, 42] Esomeprazole, the S-isomer of omeprazole, has been involved in some drug interactions,[11] but experience is limited. Overall, there are few clinically relevant drug interactions with the PPIs that involve the CYP450 isoenzymes, and none have been reported for pantoprazole and rabeprazole (see Table 6).[38, 41]

PPIs may decrease or increase the bioavailability of other drugs whose absorption is dependent on gastric pH (see Table 6). The profound inhibition of gastric acid secretion by PPIs results in decreased plasma concentrations of ampicillin, iron salts, and ketoconazole. Increases in digoxin bioavailability (area under the curve) have occurred with omeprazole (10% increase) [43] and rabeprazole (19% increase).[44]

Table 6 Selected drug interactions involving the proton pump inhibitors

Mechanism	Effect of object drug	Object drugs that may interact with the proton pump inhibitors: Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
CYP450 inhibition	↑	Clarithromycin↔ Diazepam	OCPs (?)†	Benzodiazepines Diazepam† Flurazepam Triazolam Carbamazepine† Clarithromycin↔ Cyclosporin† Disulfiram Phenytoin† Tolbutamide Warfarin†	—	—
CYP450 induction	↓	—	Theophylline	Caffeine	—	—
Decrease GI absorption	↓	Ampicillin Delavirdine† Indinavir† Iron salts Itraconazole† Ketoconazole†	Ampicillin Delavirdine† Indinavir† Iron salts Itraconazole† Ketoconazole†	Ampicillin Delavirdine† Indinavir† Iron salts Itraconazole† Ketoconazole†	Ampicillin Delavirdine† Indinavir† Iron salts Itraconazole† Ketoconazole†	Ampicillin Delavirdine† Indinavir† Iron salts Itraconazole† Ketoconazole†
Increase GI absorption	↑	—	Digoxin†	Digoxin†	—	Digoxin†

Sources: [11-15, 38, 41-48]

The list of drugs in this table is not intended to be all-inclusive. Consult appropriate references for a comprehensive list of drugs that may interact with proton pump inhibitors.

OCP = Oral contraceptive pills

† Potential clinically relevant interaction.

↔ Two-way interaction; clarithromycin may increase plasma omeprazole and esomeprazole concentrations. Omeprazole may increase plasma clarithromycin and 14-hydroxyclarithromycin concentrations. Esomeprazole may increase plasma 14-hydroxyclarithromycin concentrations.

? Unclear effect

Clinical Efficacy

The PPI doses comparable to those of lansoprazole were indirectly inferred from relative efficacies of PPIs compared primarily with omeprazole in 25 double-blind, randomized controlled trials (see Table 7). The relative efficacies were based on subjective (symptom relief) or objective (e.g., endoscopic or pH-metric) measures of response to treatment in patients with duodenal ulcers, duodenal ulcers with *Helicobacter pylori* infection, gastric ulcers, gastroesophageal reflux disease, erosive esophagitis, or dyspepsia.

Table 7 Comparable doses of PPIs

Relative efficacy of PPIs in comparison with the following doses of lansoprazole (LAN): (Doses in mg q.d.)	
LAN 15	**LAN 30**
≤ ESO 20 or 40	≤ ESO 20 or 40
≤ OME 10 or 20	≥ OME 20 or 40
= PAN 40	= PAN 40
≤ RAB 20	≤ RAB 20

Sources: [2, 7, 8, 11, 20, 22, 23, 49-66]

The comparable doses of proton pump inhibitors (PPIs) were indirectly inferred from relative efficacies reported in double-blind, randomized controlled trials in patients with gastrointestinal acid-related disorders. Most of the evaluated trials compared lansoprazole or other proton pump inhibitors (PPIs) with omeprazole. Comparable doses of lansoprazole and PPIs other than omeprazole were deduced from the direct comparisons against omeprazole. Relative efficacy was based on subjective or objective measures of response to treatment in patients with duodenal ulcers, duodenal ulcers with *Helicobacter pylori* infection, gastric ulcers, gastroesophageal reflux disease, erosive esophagitis, or dyspepsia. No trials comparing PPIs in pathologic hypersecretory conditions were found by the literature search.

ESO = Esomeprazole; LAN = Lansoprazole; OME = Omeprazole; PAN = Pantoprazole; RAB = Rabeprazole

= Comparable to

≤ Inferior or comparable to

≥ Superior or comparable to

In addition, maintenance therapy with twice daily (b.i.d) doses of lansoprazole, omeprazole, and pantoprazole were compared in a small DBRCT in patients with severe reflux esophagitis complicated by stricture.[67] This was the only DBRCT identified by the literature search that compared PPIs other than omeprazole, and in twice daily doses. Patients were first treated with omeprazole 20 mg b.i.d. (N = 36) until esophagitis was healed and symptoms of reflux and dysphagia were relieved, then they were randomized to maintenance therapy (N = 30) with either lansoprazole 30 mg, omeprazole 20 mg, and pantoprazole 40 mg each given b.i.d. After 4 weeks of treatment, omeprazole (9 of 10, 90%) was statistically significantly superior to either lansoprazole (2 of 10, 20%) or pantoprazole (3 of 10, 30%) in maintaining remission, defined as absence of esophagitis and stricture on endoscopy and absence of symptoms ($p < 0.01$ for each analysis). No statistically significant difference was noted between lansoprazole and pantoprazole. The authors attributed the treatment differences to intra- and interindividual variability in lansoprazole absorption and to pH-dependent differences in reactivity between omeprazole and pantoprazole in inhibiting H+/K+-ATPase. Further clinical trials in large patient populations are needed to evaluate relative antisecretory efficacies of PPIs given twice daily.

Conclusion

The PPIs may be considered for therapeutic interchange because of their comparable pharmacologic properties and clinical efficacy and safety profiles. Consistent results of clinical trials in patients with duodenal ulcers, gastric ulcers, GERD, hypersecretory conditions, and other acid-related disorders strongly suggest that there is a class effect of PPIs for these disorders, although differences in dosage formulations and drug interactions may occasionally influence choice of PPI in individual cases.

References

1. Bianchi Porro G, Lazzaroni M, Imbesi V, Montrone F, Santagada T. Efficacy of pantoprazole in the prevention of peptic ulcers, induced by non-steroidal anti-inflammatory drugs: a prospective, placebo-controlled, double-blind, parallel-group study. *Dig Liver Dis* 2000;32:201-8.
2. Witzel L, Gutz H, Huttemann W, Schepp W. Pantoprazole versus omeprazole in the treatment of acute gastric ulcers. *Aliment Pharmacol Ther* 1995;9:19-24.
3. Meneghelli UG, Zaterka S, de Paula Castro L, Malafaia O, Lyra LG. Pantoprazole versus ranitidine in the treatment of duodenal ulcer: a multicenter study in Brazil. *Am J Gastroenterol* 2000;95:62-6.
4. Chen TS, Chang FY, Ng WW, Lee FY, Hwang SJ, Lee SD. The efficacy of the third pump inhibitor--pantoprazole--in the short-term treatment of Chinese patients with duodenal ulcer. *Hepatogastroenterology* 1999;46:2372-8.
5. Cremer M, Lambert R, Lamers CB, Delle Fave G, Maier C. A double-blind study of pantoprazole and ranitidine in treatment of acute duodenal ulcer. A multicenter trial. European Pantoprazole Study Group. *Dig Dis Sci* 1995;40:1360-4.
6. Schepp W, Classen M. Pantoprazole and ranitidine in the treatment of acute duodenal ulcer. A multicentre study. *Scand J Gastroenterol* 1995;30:511-4.
7. Rehner M, Rohner HG, Schepp W. Comparison of pantoprazole versus omeprazole in the treatment of acute duodenal ulceration--a multicentre study. *Aliment Pharmacol Ther* 1995;9:411-6.
8. Beker JA, Bianchi Porro G, Bigard MA et al. Double-blind comparison of pantoprazole and omeprazole for the treatment of acute duodenal ulcer. *Eur J Gastroenterol Hepatol* 1995;7:407-10.
9. Judmaier G, Koelz HR. Comparison of pantoprazole and ranitidine in the treatment of acute duodenal ulcer. Pantoprazole-Duodenal Ulcer-Study Group. *Aliment Pharmacol Ther* 1994;8:81-6.
10. Anonymous. Drug Facts and Comparisons. St. Louis: Facts and Comparisons® A Wolters Kluwer Co; 2001.
11. AstraZeneca. Nexium [package insert]. Wilmington, DE: AstraZeneca LP; 2001.
12. Wyeth-Ayerst. Protonix [package insert]. Philadelphia, PA: Wyeth-Ayerst. 2000.
13. Eisai. Aciphex [package insert]. Misato, Japan: Eisai Co., Ltd. 1999.
14. AstraZeneca. Prilosec [package insert]. Wilmington, DE: AstraZeneca LP. 2000.
15. TAP. Prevacid [package insert]. Lake Forest, IL: TAP Pharmaceuticals Inc. 2000.
16. Anonymous. Omeprazole: Laryngitis. *In: Off-Label Drug Facts*. St. Louis: Facts and Comparisons® , A Wolters Kluwer Co.; 2001:367-71.

17. Richter JE, Bochenek W. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. Pantoprazole US GERD Study Group. *Am J Gastroenterol* 2000;95:3071-80.

18. van Zyl JH, de KGH, van Rensburg CJ et al. Efficacy and tolerability of 20 mg pantoprazole versus 300 mg ranitidine in patients with mild reflux-oesophagitis: a randomized, double-blind, parallel, and multicentre study. *Eur J Gastroenterol Hepatol* 2000;12:197-202.

19. Koop H, Schepp W, Dammann HG, Schneider A, Luhmann R, Classen M. Comparative trial of pantoprazole and ranitidine in the treatment of reflux esophagitis. Results of a German multicenter study. *J Clin Gastroenterol* 1995;20:192-5.

20. Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to omeprazole, 20 mg once daily, in the healing of erosive gastrooesophageal reflux disease. *Scand J Gastroenterol* 2000;35:1245-50.

21. Farley A, Wruble LD, Humphries TJ. Rabeprazole versus ranitidine for the treatment of erosive gastroesophageal reflux disease: a double-blind, randomized clinical trial. Rabeprazole Study Group. *Am J Gastroenterol* 2000;95:1894-9.

22. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Double-blind comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-esophageal reflux disease. The European Rabeprazole Study Group. *Aliment Pharmacol Ther* 1999;13:49-57.

23. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of active gastric ulcer--a European multicentre study. The European Rabeprazole Study Group. *Aliment Pharmacol Ther* 1998;12:789-95.

24. Cammarota G, Cianci R, Cannizzaro O et al. Efficacy of two one-week rabeprazole/levofloxacin-based triple therapies for Helicobacter pylori infection. *Aliment Pharmacol Ther* 2000;14:1339-43.

25. Humphries TJ, Rindi G, Fiocca R. Pilot studies on the effects of rabeprazole sodium (E3810), amoxicillin, and placebo on the eradication on *H. pylori*. *Am J Gastroenterol* 1996;91:1914.

26. Kihira K, Satoh K, Saifuku K et al. Rabeprazole, amoxycillin and low- or high-dose clarithromycin for cure of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2000;14:1083-7.

27. Lueth S, Teyssen S, Singer M. A four day triple therapy with rabeprazole, amoxycillin and clarithromycin in patients with peptic ulcer disease and *Helicobacter pylori* infection is safe and effective in 90%--a pilot study (abstract). *Am J Gastroenterol* 2000;95:2435.

28. Miwa H, Ohkura R, Murai T et al. Impact of rabeprazole, a new proton pump inhibitor, in triple therapy for Helicobacter pylori infection-comparison with omeprazole and lansoprazole. *Aliment Pharmacol Ther* 1999;13:741-6.

29. Miwa H, Yamada T, Sato K et al. Efficacy of reduced dosage of rabeprazole in PPI/AC therapy for Helicobacter pylori infection: comparison of 20 and 40 mg rabeprazole with 60 mg lansoprazole. *Dig Dis Sci* 2000;45:77-82.

30. Nagahara A, Miwa H, Ogawa K et al. Addition of metronidazole to rabeprazole-amoxicillin-clarithromycin regimen for Helicobacter pylori infection provides an excellent cure rate with five-day therapy. *Helicobacter* 2000;5:88-93.

31. Nagahara A, Miwa H, Yamada T, Kurosawa A, Ohkura R, Sato N. Five-day proton pump inhibitor-based quadruple therapy regimen is more effective than 7-day triple therapy regimen for Helicobacter pylori infection. *Aliment Pharmacol Ther* 2001;15:417-21.

32. Stack WA, Knifton A, Thirlwell D et al. Safety and efficacy of rabeprazole in combination with four antibiotic regimens for the eradication of Helicobacter pylori in patients with chronic gastritis with or without peptic ulceration. *Am J Gastroenterol* 1998;93:1909-13.

33. Miner P, Fillipone J, Jokubaitis L, et al. Rabeprazole results in global improvement in symptoms of nonerosive gastroesophageal reflux disease. *Am J Gastroenterol* 2000;95:A2435.

34. Miner P, Fillipone J, Jokubaitis L, et al. Rabeprazole relieves heartburn and associated symptoms in nonerosive gastroesophageal reflux disease. *Am J Gastroenterol* 2000;95:A2435.

35. Miner P, Sloan S, Fillipone J, et al. Significant heartburn relief after the first dose of rabeprazole sodium in non-erosive reflux disease (NERD) patients. *Gastroenterology* 2000;118:A338.

36. Mohiuddin MA, Pursnani KG, Katzka DA, Gideon RM, Castell JA, Castell DO. Effective gastric acid suppression after oral administration of enteric- coated omeprazole granules. *Dig Dis Sci* 1997;42:715-9.

37. Phillips JO, Metzler MH, Johnson M. The stability of simplified omeprazole suspension (SOS) (abstract). *Critical Care Medicine* 1998;28:A221.

38. Stedman CA, Barclay ML. Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. *Aliment Pharmacol Ther* 2000;14:963-78.

39. Humphries TJ. Clinical implications of drug interactions with the cytochrome P-450 enzyme system associated with omeprazole. *Dig Dis Sci* 1991;36:1665-9.

40. VandenBranden M, Ring BJ, Binkley SN, Wrighton SA. Interaction of human liver cytochromes P450 in vitro with LY307640, a gastric proton pump inhibitor. *Pharmacogenetics* 1996;6:81-91.

41. Lew EA. Review article: pharmacokinetic concerns in the selection of anti-ulcer therapy. *Aliment Pharmacol Ther* 1999;13 Suppl 5:11-6.

42. Humphries TJ, Merritt GJ. Review article: drug interactions with agents used to treat acid- related diseases. *Aliment Pharmacol Ther* 1999;13 Suppl 3:18-26.

43. Oosterhuis B, Jonkman JH, Andersson T, Zuiderwijk PB, Jedema JN. Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. *Br J Clin Pharmacol* 1991;32:569-72.

44. Humphries TJ, Spera AC, Laurent AL, Spanyers SA. Coadministration of rabeprazole sodium (E3810) and digoxin results in a predictable interaction (abstract). *Am J Gastroenterol* 1996;91:1914.

45. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. *Clin Pharmacokinet* 1996;31:9-28.

46. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors--emphasis on rabeprazole. *Aliment Pharmacol Ther* 1999;13 Suppl 3:27-36.

47. Michalets EL. Update: Clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy* 1998;18:84-112.

48. Hansten PD, Horn JR. Drug Interactions: Analysis and Management. St. Louis, MO: Facts & Comparisons; 2001.

49. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Comparison of rabeprazole 20 mg versus omeprazole 20 mg in the treatment of active duodenal ulcer: a European multicentre study. *Aliment Pharmacol Ther* 1999;13:179-86.

50. Poynard T, Lemaire M, Agostini H. Meta-analysis of randomized clinical trials comparing lansoprazole with ranitidine or famotidine in the treatment of acute duodenal ulcer. *Eur J Gastroenterol Hepatol* 1995;7:661-5.

51. Chang FY, Chiang CY, Tam TN, Ng WW, Lee SD. Comparison of lansoprazole and omeprazole in the short-term management of duodenal ulcers in Taiwan. *J Gastroenterol Hepatol* 1995;10:595-601.

52. Ekstrom P, Carling L, Unge P, Anker-Hansen O, Sjostedt S, Sellstrom H. Lansoprazole versus omeprazole in active duodenal ulcer. A double-blind, randomized, comparative study. *Scand J Gastroenterol* 1995;30:210-5.

53. Dobrilla G, Piazzi L, Fiocca R. Lansoprazole versus omeprazole for duodenal ulcer healing and prevention of relapse: a randomized, multicenter, double-masked trial. *Clin Ther* 1999;21:1321-32.

54. Sito E, Konturek PC, Bielanski W et al. One week treatment with omeprazole, clarithromycin and tinidazole or lansoprazole, amoxicillin and metronidazole for cure of Helicobacter pylori infection in duodenal ulcer patients. *J Physiol Pharmacol* 1996;47:221-8.

55. Lind T, Rydberg L, Kyleback A et al. Esomeprazole provides improved acid control vs. omeprazole In patients with symptoms of gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics* 2000;14:861-7.

56. Janczewska I, Sagar M, Sjostedt S, Hammarlund B, Iwarzon M, Seensalu R. Comparison of the effect of lansoprazole and omeprazole on intragastric acidity and gastroesophageal reflux in patients with gastroesophageal reflux disease. *Scand J Gastroenterol* 1998;33:1239-43.

57. Richter JE, Kahrilas PJ, Johanson J et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *Am J Gastroenterol* 2001;96:656-65.

58. Kahrilas PJ, Falk GW, Johnson DA et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: A randomized controlled trial. *Alimentary Pharmacology & Therapeutics* 2000;14:1249-1258.

59. Chiba N. Proton pump inhibitors in acute healing and maintenance of erosive or worse esophagitis: a systematic overview. *Can J Gastroenterol* 1997;11 Suppl B:66B-73B.

60. Hatlebakk JG, Berstad A, Carling L et al. Lansoprazole versus omeprazole in short-term treatment of reflux oesophagitis. Results of a Scandinavian multicentre trial. *Scand J Gastroenterol* 1993;28:224-8.

61. Mee AS, Rowley JL. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. *Aliment Pharmacol Ther* 1996;10:757-63.

62. Mossner J, Holscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. *Aliment Pharmacol Ther* 1995;9:321-6.

63. Mulder CJ, Dekker W, Gerretsen M. Lansoprazole 30 mg versus omeprazole 40 mg in the treatment of reflux oesophagitis grade II, III and IVa (a Dutch multicentre trial). Dutch Study Group. *Eur J Gastroenterol Hepatol* 1996;8:1101-6.

64. Sharma VK, Leontiadis GI, Howden CW. Meta-analysis of randomized controlled trials comparing standard clinical doses of omeprazole and lansoprazole in erosive oesophagitis. *Aliment Pharmacol Ther* 2001;15:227-31.

65. Thjodleifsson B, Beker JA, Dekkers C, Bjaaland T, Finnegan V, Humphries TJ. Rabeprazole versus omeprazole in preventing relapse of erosive or ulcerative gastroesophageal reflux disease: a double-blind, multicenter, European trial. The European Rabeprazole Study Group. *Dig Dis Sci* 2000;45:845-53.

66. Jones R, Crouch SL. Low-dose lansoprazole provides greater relief of heartburn and epigastric pain than low-dose omeprazole in patients with acid-related dyspepsia. *Aliment Pharmacol Ther* 1999;13:413-9.

67. Jaspersen D, Diehl KL, Schoeppner H, Geyer P, Martens E. A comparison of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis. *Aliment Pharmacol Ther* 1998;12:49-52.