Therapeutic Class Overview
Proton Pump Inhibitors Single Entity Agents

Therapeutic Class

- The proton-pump inhibitors (PPIs) suppress gastric acid secretion and are generally considered the most potent acid suppressants available.[1] Within the parietal cells of the gastric mucosa, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K+) for hydrogen ions (H+) resulting in a lower gastric pH. The PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. The PPIs can only inhibit proton pumps that are actively secreting acid.[1] Approximately 70 to 80% of the proton pumps will be active following a meal.[2] As a result, single doses of PPIs will not completely inhibit acid secretion and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. With regular dosing, maximal acid suppression occurs in three to four days.[1-3]

  There are currently six PPIs available on the market in a variety of formulations. The PPIs include dexlansoprazole (Dexilant®), esomeprazole (Nexium®), lansoprazole (Prevacid®, Prevacid SoluTab®, Prevacid® 24HR), omeprazole (Prilosec®, Prilosec OTC®, Zegerid®, Zegerid OTC®), pantoprazole (Protonix®) and rabeprazole (Aciphex®), of which lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are available generically.[4-15] In addition, lansoprazole, omeprazole and omeprazole with sodium bicarbonate are available over-the-counter.[4] All of the PPIs are substituted benzimidazole derivatives and are structurally related. Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole contains only the *S*-isomers of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer. The PPIs primarily differ in their pharmacokinetic and pharmacodynamic properties in addition to their formulations. While some differences have been reported in head-to-head studies directly comparing the PPIs, the magnitude of these differences is generally small and the clinical significance has not been established.[3] When administered in equivalent dosages, the PPIs have generally demonstrated a comparable efficacy to one another. Dexlansoprazole, the enantiomer of lansoprazole, is the first PPI with a dual delayed-release formulation designed to provide two separate releases of medication. It contains two types of enteric-coated granules resulting in a concentration-time profile with two distinct peaks: the first peak occurs one to two hours after administration, followed by a second peak within four to five hours. In addition, it can be taken regardless of meals.[15] All approved indications listed in Table 1 are for the prescription products unless otherwise specified.

Table 1. Current Medications Available in the Class[4-15]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Dexlansoprazole (Dexilant®)	Treatment of erosive esophagitis, maintaining healing of erosive esophagitis, treatment of symptomatic gastroesophageal reflux disease	Delayed-release capsule: 30 mg 60 mg	-
Esomeprazole magnesium (Nexium®)	Treatment of erosive esophagitis, maintaining healing of erosive esophagitis†, treatment of symptomatic gastroesophageal reflux disease†, *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence†§, risk reduction of nonsteroidal antiinflammatory drug-associated gastric ulcer†, treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome†	Delayed-release capsule: 20 mg 40 mg Delayed-release suspension: 2.5 mg 5 mg 10 mg 20 mg 40 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Esomeprazole sodium (Nexium IV®)	Treatment of erosive esophagitis	Solution for injection: 20 mg 40 mg	-
Lansoprazole (Prevacid®*, Prevacid SoluTab®*, Prevacid® 24HR*)	Treatment of erosive esophagitis, maintaining healing of erosive esophagitis, treatment of symptomatic gastroesophageal reflux disease, *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence§, treatment of active duodenal ulcers, maintenance of healing duodenal ulcers, treatment of active, benign gastric ulcer, healing of nonsteroidal anti-inflammatory drug-associated gastric ulcer, risk reduction of nonsteroidal antiinflammatory drug-associated gastric ulcer, treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome, treatment of frequent heartburn for up to 14 days¶	Delayed-release capsule: 15 mg 30 mg Delayed-release capsule (OTC): 15 mg Delayed-release disintegrating tablet: 15 mg 30 mg	a
Omeprazole (Prilosec®*)	Treatment of erosive esophagitis, maintaining healing of erosive esophagitis, treatment of symptomatic gastroesophageal reflux disease, *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence§, treatment of active duodenal ulcers, treatment of active, benign gastric ulcer, treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome	Delayed-release capsule: 10 mg 20 mg 40 mg Delayed-release tablet (OTC): 20 mg	a
Omeprazole magnesium (Prilosec®*, Prilosec OTC®*)	Treatment of erosive esophagitis, maintaining healing of erosive esophagitis, treatment of symptomatic gastroesophageal reflux disease, *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence§, treatment of active duodenal ulcers, treatment of active, benign gastric ulcer, treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome, treatment of frequent heartburn for up to 14 days¶	Delayed-release capsule (OTC): 20.6 mg Delayed-release tablet (OTC): 20 mg Delayed-release suspension: 2.5 mg 10 mg	a
Omeprazole with sodium bicarbonate (Zegerid®*, Zegerid OTC®*)	Risk reduction of upper gastrointestinal bleeding in critically ill patients‖, Treatment of frequent heartburn for up to 14 days¶	Capsule: 20 mg 40 mg Capsule (OTC): 20 mg Powder for oral suspension: 20 mg 40 mg	a
Pantoprazole (Protonix®*, Protonix IV®)	Treatment of erosive esophagitis, maintaining healing of erosive esophagitis, treatment of symptomatic gastroesophageal reflux disease‡,	Delayed-release suspension: 40 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome	Delayed-release tablet: 20 mg 40 mg Solution for injection: 40 mg	
Rabeprazole (Aciphex®)	Treatment of erosive esophagitis, maintaining healing of erosive esophagitis, treatment of symptomatic gastroesophageal reflux disease, *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence§, treatment of active duodenal ulcers, treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome	Delayed-release tablet: 20 mg	-

OTC=over the counter
*Generic available in at least one dosage form or strength.
† Oral formulations only.
‡ Intravenous formulation indicated for treatment of gastroesophageal reflux disease associated with a history of erosive esophagitis.
§ As triple therapy in combination with amoxicillin and clarithromycin (esomeprazole, lansoprazole, omeprazole and rabeprazole) or dual therapy with amoxicillin (lansoprazole) or clarithromycin (omeprazole).
‖ Zegerid® powder for oral suspension only.
¶ Over-the counter formulation only.

Evidence-based Medicine

- Meta-analyses and head-to-head trials have demonstrated comparable healing rates, maintenance of healing or symptomatic relief of gastroesophageal reflux disease (GERD) between lansoprazole, omeprazole, pantoprazole and rabeprazole.[16-21]
- The results of several meta-analyses and clinical trials show that esomeprazole may provide higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole and pantoprazole at four and eight weeks; however, the differences between treatments were generally small and the clinical significance of such differences has not been established.[16,18,22-27]
- Dexlansoprazole has been shown to significantly improve control of heartburn symptoms, nighttime heartburn symptoms, and healing of erosive esophagitis compared to placebo.[28-30] Head to head studies comparing dexlansoprazole to other proton pump inhibitors (PPIs) are limited.
- Meta-analyses and head-to-head trials comparing PPIs for the treatment of peptic ulcer disease with *Helicobacter pylori* have shown comparable rates of eradication when paired with comparable antibiotic regimens.[31-39] One small trial reported higher eradication rates for patients treated with esomeprazole compared to pantoprazole.[40] In a recent meta-analysis by McNicholl et al, both esomeprazole- and rabeprazole-based *Helicobacter pylori* regimens were considered to be more effective with regard to eradication rate compared to traditional PPIs (lansoprazole, omeprazole and pantoprazole).[41]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Acid suppression is the mainstay of gastroesophageal reflux disease (GERD) therapy and proton-pump inhibitors (PPIs) provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients. Histamine H_2-receptor antagonists (H_2RAs) given in divided doses may be effective in some patients with less severe GERD; however, they are less effective compared to the PPIs.[42,43]

- Twice-daily PPI therapy is recommended in patients with an inadequate symptom response to once-daily PPI therapy. There is no evidence of improved efficacy by adding a nocturnal dose of an H_2RA to twice-daily PPI therapy.[42,43]
- In the management of dyspepsia, treatment with a PPI for four to eight weeks as an initial therapy option is recommended in dyspeptic patients ≤55 years of age without alarm features (e.g., bleeding, dysphagia, family history of gastrointestinal cancer, weight loss) and where *Helicobacter pylori* prevalence is low (<10%).[44]
- The recommended primary therapies for *H pylori* infection include a PPI, clarithromycin and amoxicillin or metronidazole (clarithromycin-based triple therapy) for 14 days for eradication rates of 70 to 85%. Alternatively, a regimen of a PPI or H_2RA, bismuth, metronidazole and tetracycline (bismuth-based quadruple therapy) for 10 to 14 days produces eradication rates of 75 to 90%.[45]
- The currently available PPIs perform comparably when used in the triple therapy regimens. A meta-analysis of 13 studies suggests that twice daily dosing of a PPI (lansoprazole, omeprazole, pantoprazole and rabeprazole) in clarithromycin-based triple regimens is more effective than once-daily dosing.[45]
- Attempts to eliminate esophageal acid exposure (PPIs in doses greater than once-daily, esophageal pH monitoring to titrate PPI dosing, or antireflux surgery) for the prevention of esophageal adenocarcinoma is not recommended.[46]

· Other Key Facts:
- Currently, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are available generically.[4]
- Furthermore, lansoprazole, omeprazole and omeprazole with sodium bicarbonate are available over-the-counter in a variety of formulations.[4]
- Dexlansoprazole was formerly known by the brand name Kapidex® but has since been changed to Dexilant®.[46]

References

1. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology. 2000;118(2 Suppl 1):S9-31.
2. Welage LS. Pharmacologic features of proton-pump inhibitors and their potential relevance to clinical practice. Gastroenterol Clin North Am. 2003;32(3 Suppl):S25-35.
3. Wolfe MM. Overview and comparison of the proton-pump inhibitors for the treatment of acid-related disorders. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Sept 12]. Available from: http://www.utdol.com/online/content/topic.do?topicKey=acidpep/10094&selectedTitle=1~150&source=search_result.
4. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2012 [cited 2012 Sept 12]. Available from: http://online.factsandcomparisons.com.
5. Aciphex® [package insert].Woodcliff Lake (NJ): Eisai Inc.; 2012 May.
6. Nexium® [package insert]. Wilmington (DE): AstraZeneca LP; 2012 Jan.
7. Nexium® IV [package insert]. Wilmington (DE): AstraZeneca LP; 2012 Jan.
8. Prevacid® [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2012 May.
9. Prevacid® OTC [product label]. Basal (Switzerland): Novartis Consumer Health, Inc.; 2009 Aug.
10. Prilosec® [package insert]. Wilmington (DE): AstraZeneca LP; 2012 Feb.
11. Prilosec® OTC [product label]. Cincinnati (OH): Procter and Gamble; 2011 Aug.
12. Protonix® [package insert]. Philadelphia (PA): Wyeth Pharmaceuticals Inc.; 2012 May.
13. Protonix® IV [package insert].Philadelphia (PA): Wyeth Pharmaceuticals Inc.; 2012 May.
14. Zegerid® [package insert]. San Diego (CA): Santarus Inc.; 2011 May.
15. Dexilant® [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2012 May.
16. Klok RM, Postma MJ, van Hout BA, Brouwers JR. Meta-analysis: comparing the efficacy of proton-pump inhibitors in short-term use. Aliment Pharmacol Ther. 2003;17(10):1237-45.
17. Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared to omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. Clin Ther. 2001;23(7):998-1017.
18. Edwards SJ, Lind T, Lundell L. Systematic review of proton-pump inhibitors for the acute treatment of reflux oesophagitis. Aliment Pharmacol Ther. 2001;15(11):1729-36.
19. 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(2):227-31.
20. Bardhan KD, Van Rensburg C. Comparable clinical efficacy and tolerability of 20 mg pantoprazole and 20 mg omeprazole in patients with grade I reflux oesophagitis. Aliment Pharmacol Ther. 2001;15:1585-91.
21. Pace F, Annese V, Prada A, Zambelli A, Casalini S, Nardini P, et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomized, double-blind, comparative study of rabeprazole and omeprazole

20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Dig Liver Dis. 2005;37:741-50.
22. Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S, et al. Esomeprazole (40 mg) compared to lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002;97:575-83.
23. Devault KR, Johanson JF, Johnson DA, Liu S, Sostek MB. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. Clin Gastroenterol Hepatol. 2006 Jul;4(7):852-9.
24. Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, et al. Efficacy and safety of esomeprazole compared to omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol. 2001;96:656-65.
25. Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, et al. Esomeprazole improves healing and symptom resolution as compared to omeprazole in reflux oesophagitis patients: a randomized controlled trial. Aliment Pharmacol Ther. 2000;14:1249-58.
26. Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, et al. A randomized comparative study of esomeprazole 40 mg vs pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther. 2005;21(6):739-46.
27. Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, et al. Esomeprazole 20 mg vs pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. Aliment Pharmacol Ther. 2005 Nov 1;22(9):803-11.
28. Fass R, Inadomi J, Han C, Mody R, O'Neil J, Perez MC. Maintenance of heartburn relief after step-down from twice-daily proton pump inhibitor to once-daily dexlansoprazole modified release. Clin Gastroenterol Hepatol. 2012 Mar;10(3):247-53.
29. Fass R, Johnson DA, Orr WC, Han C, Mody R, Stern KN, et al. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. Am J Gastroenterol. 2011 Mar;106(3):421-31.
30. Howden CW, Larsen LM, Perez MC, Palmer R, Atkinson SN. Clinical trial: efficacy and safety of dexlansoprazole MR 60 and 90 mg in healed erosive oesophagitis – maintenance of healing and symptom relief. Aliment Pharmacol Ther. 2009;30:895-907.
31. Choi HS, Park DI, Hwang SJ, Park JS, Kim HJ, Cho YK, et al. Double-dose, new-generation proton-pump inhibitors do not improve eradication rate. Helicobacter. 2007;2(6):638-42.
32. Vergara M, Vallve M, Gisbert JP, Calvet X. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003;18:647-54.
33. Ulmer HJ, Beckerling A, Gatz G. Recent use of proton-pump inhibitor-based triple therapies for the eradication of H pylori: a broad data review. Helicobacter. 2003;8(2):95-104.
34. Gisbert JP, Pajares JM. Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis. Dig Liver Dis. 2004;36(4)253-9.
35. Wang X, Fang JY, Lu R, Sun DF. A meta-analysis: comparison of esomeprazole and other proton-pump inhibitors in eradicating Helicobacter pylori. Digestion. 2006;73(2-3):178-86.
36. Wu IC, Wu DC, Hsu PI, Lu CY, Yu FJ, Wang TE, et al. Rabeprazole- vs esomeprazole-based eradication regimens for H pylori infection. Helicobacter. 2007;12(6):633-7.
37. Bazzoli F, Pozzato P, Zagari M, Fossi S, Ricciardiello L, Nicolini G, et al. Efficacy of lansoprazole in eradicating Helicobacter pylori: a meta-analysis. Helicobacter. 1998;3(3):195-201.
38. Gisbert JP, Khorrami S, Calvet X, Pajares JM. Pantoprazole-based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2004;16(1):89-99.
39. Gisbert JP, Khorrami S, Calvet X, Pajares JM. Systematic review: rabeprazole-based therapies in Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003;17(6):751-64.
40. Hsu PI, Lai KH, Lin CK, Chen WC, Yu HC, Cheng JS, et al. A prospective randomized trial of esomeprazole-vs pantoprazole-based triple therapy for Helicobacter pylori eradication. Am J Gastroenterol. 2005;100(11):2387-92.
41. McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. Aliment Pharmacol Ther. 2012 Sep;36(5):414-25.
42. DeVault KR, Castell DO; American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 2005;100(1):190-200.
43. Kahrilas PJ, Shaheen NJ, Vaezi MF, Hiltz SW, Black E, Modlin IM, et al; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology. 2008 Oct;135(4):1383-91,1391.e1-5.
44. Talley NJ, Vakil N; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005;100(10):2324-37.
45. Chey WD, Wong BCY and the Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology Guideline on the management of Helicobacter pylori infection. Am J Gastroenterol. 2007;102:1808-25.
46. American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011 Mar;140(3):1084-91.
47. Kapidex® (dexlansoprazole) renamed Dexilant® in U.S. to avoid name confusion [press release on the internet]. Takeda Pharmaceuticals North America, Inc. 2010 Mar 4 [cited 2012 Sep 12]. Available from: http://www.takeda.us/newsroom/press_release_detail.aspx?year=2010&id=114.

Therapeutic Class Review
Proton Pump Inhibitors Single Entity Agents

Overview/Summary

The proton-pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally considered the most potent acid suppressants available.[1] Parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to several stimuli. Within the parietal cell, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K+) for hydrogen ions (H+) resulting in a lower gastric pH. The PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. The PPIs can only inhibit proton pumps that are actively secreting acid.[1] Approximately 70 to 80% of the proton pumps will be active following a meal.[2] As a result, single doses of PPIs will not completely inhibit acid secretion and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. With regular dosing, maximal acid suppression occurs in three to four days.[1-3]

There are currently six PPIs available on the market in a variety of formulations. The PPIs include dexlansoprazole (Dexilant®), esomeprazole (Nexium®), lansoprazole (Prevacid®, Prevacid SoluTab®, Prevacid® 24HR), omeprazole (Prilosec®, Prilosec OTC®, Zegerid®, Zegerid OTC®), pantoprazole (Protonix®) and rabeprazole (Aciphex®), of which lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are available generically.[4-15] In addition, lansoprazole and omeprazole are available over-the-counter in a variety of formulations. All of the PPIs are substituted benzimidazole derivatives and are structurally related. Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole contains only the *S*-isomers of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer. The PPIs primarily differ in their pharmacokinetic and pharmacodynamic properties in addition to their formulations. While some differences have been reported in head-to-head studies directly comparing the PPIs, the magnitude of these differences is generally small and the clinical significance has not been established.[3] When administered in equivalent dosages the PPIs have generally demonstrated a comparable efficacy to one another.

The newest agent in the class, dexlansoprazole (Dexilant®), is Food and Drug Administration approved for the treatment of erosive esophagitis as well as heartburn associated with non-erosive gastroesophageal reflux disease (GERD). This agent was formerly known by the brand name Kapidex® but has since been changed to Dexilant®.[16] Dexlansoprazole, the enantiomer of lansoprazole, is the first PPI with a dual delayed-release formulation designed to provide two separate releases of medication. It contains two types of enteric-coated granules resulting in a concentration-time profile with two distinct peaks: the first peak occurs one to two hours after administration, followed by a second peak within four to five hours. In addition, it can be taken regardless of meals.[15]

Current national and international consensus guidelines recognize the PPIs as first-line therapy for the management of dyspepsia, GERD, peptic ulcer disease and eradication of *Helicobacter pylori.*[17-24] In addition, these agents have a role in the management of Barrett's Esophagus.[25,26] Currently available guidelines do not give preference to one PPI over another.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Dexlansoprazole (Dexilant®)	Proton-pump inhibitor	-
Esomeprazole magnesium (Nexium®)	Proton-pump inhibitor	-
Esomeprazole sodium (Nexium IV®)	Proton-pump inhibitor	-
Lansoprazole (Prevacid®*, Prevacid SoluTab®*,	Proton-pump inhibitor	a

Generic Name (Trade name)	Medication Class	Generic Availability
Prevacid®* 24HR)		
Omeprazole (Prilosec®*)	Proton-pump inhibitor	a
Omeprazole magnesium (Prilosec®*, Prilosec OTC®*)	Proton-pump inhibitor	a
Omeprazole with sodium bicarbonate (Zegerid®*, Zegerid OTC®*)	Proton-pump inhibitor	a
Pantoprazole (Protonix®*, Protonix IV®)	Proton-pump inhibitor	a
Rabeprazole (Aciphex®)	Proton-pump inhibitor	-

*Generic is available in at least one dosage form or strength.

Indications

In general, treatment of any of the Food and Drug Administration approved indications listed in Table 2 is for short-term. In some cases, a different dosage and/or length of therapy may be indicated for the maintenance treatment of a particular acid-related disorder. All approved indications are for the prescription products unless otherwise specified.

Table 2. Food and Drug Administration Approved Indications[4-15]

Indication	Dexlansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Gastroesophageal Reflux Disease						
Treatment of erosive esophagitis	a	a	a	a	a	a
Maintaining healing of erosive esophagitis	a	a *	a	a	a	a
Treatment of symptomatic gastroesophageal reflux disease	a	a *	a	a	a †	a
Peptic Ulcer Disease						
Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence		a *‡	a ‡	a ‡ (Prilosec®)		a ‡
Treatment of active duodenal ulcers			a	a		a
Maintenance of healing duodenal ulcers			a			
Treatment of active, benign gastric ulcer			a	a		
Healing of nonsteroidal anti-inflammatory drug-associated gastric ulcer			a			
Risk reduction of nonsteroidal antiinflammatory drug-associated gastric ulcer		a *	a			
Other						
Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome		a *	a	a	a	a
Risk reduction of upper gastrointestinal bleeding in critically ill patients				a (Zegerid®§)		
Treatment of frequent heartburn for up to 14 days			a (Prevacid® 24HR)	a (Prilosec OTC®, Zegerid OTC®)		

*Oral formulations only.

†Intravenous formulation indicated for treatment of gastroesophageal reflux disease associated with a history of erosive esophagitis.
‡As triple therapy in combination with amoxicillin and clarithromycin (esomeprazole, lansoprazole, omeprazole and rabeprazole) or dual therapy with amoxicillin (lansoprazole) or clarithromycin (omeprazole).
§Zegerid® powder for oral suspension only.

In addition to their respective Food and Drug Administration-approved indication, the proton pump inhibitors as a class are consistently used off-label as treatment for stress ulcer prophylaxis in critically ill patients and in the prevention of gastrointestinal bleeding in high-risk patients receiving antiplatelet therapy.[4]

Pharmacokinetics

Pharmacokinetic differences exist between the proton-pump inhibitors (PPIs), particularly with regard to bioavailability and metabolism. While they are all hepatically metabolized, the PPIs are metabolized by different pathways within the cytochrome P450 (CYP) enzyme system. The relative importance of the CYP2C19 pathway on the metabolism of PPIs has been reported to be omeprazole = esomeprazole > pantoprazole > lansoprazole > rabeprazole.[27] Depending upon their CYP2C19 genotype, patients may be considered extensive, intermediate or poor metabolizers. Approximately 67% of Caucasians are extensive metabolizers and approximately 5% are slow metabolizers.[3] Some studies have reported higher cure rates for gastroesophageal reflux disease and eradication of *Helicobacter pylori* in patients who were poor metabolizers.[3,27] Additional studies are needed before definitive conclusions can be made regarding the use of certain PPIs in specific patient populations.

Table 3. Pharmacokinetics[4-15,28]

Generic Name	Bioavailability (%)	Time to Peak Concentration (hours)	Renal Excretion (%)	Hepatic Metabolism (active metabolites)	Serum Half-Life (hours)
Dexlansoprazole	Not reported	1 to 2	50.7	CYP2C19, CYP3A4 (none)	1 to 2
Esomeprazole magnesium	90	1.5	80	CYP2C19, CYP3A4 (none)	1.0 to 1.5
Esomeprazole sodium	100	Not reported	80	CYP2C19, CYP3A4 (none)	1.05 to 1.41
Lansoprazole	81 to 91	1.7	14 to 25	CYP2C19, CYP3A4 (cyclic sulfenamide and disulfide metabolites)	0.9 to 1.5
Omeprazole	30 to 40	0.5 to 3.5	77	CYP2C19 (none)	0.5 to 1.0
Omeprazole magnesium	Not reported	Not reported	Not reported	CYP2C19 (none)	0.5 to 1.0
Omeprazole with sodium bicarbonate	30 to 40 (suspension)	0.5	77	CYP2C19 (none)	1
Pantoprazole	77	2.5	71	CYP2C19, CYP3A4 (not reported)	1
Rabeprazole	~52	2 to 5	90	CYP2C19, CYP3A4 (not reported)	1 to 2

Clinical Trials

Clinical trials have consistently demonstrated that proton-pump inhibitors (PPIs) are highly effective in treating, providing symptomatic relief and preventing relapse in gastric acid disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease.[29-86]

In meta-analyses and direct comparator trials, lansoprazole, omeprazole, pantoprazole and rabeprazole have demonstrated comparable healing rates, maintenance of healing or symptomatic relief of GERD.[30-32,56,60,62] Richter et al reported that lansoprazole produced a significantly quicker and greater symptomatic

relief of GERD compared to omeprazole; however, the absolute differences in this trial were small and the clinical impact of the difference was not measured within the trial.[57]

The results of several meta-analyses and clinical trials show that esomeprazole may provide higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole and pantoprazole at four and eight weeks.[30,32,40,42,46,48,51,52] Subgroup analyses in a few trials noted higher healing rates with esomeprazole in patients with more severe disease.[49,51] Close analyses of all of these studies show that the overall differences between treatments were generally small and the clinical significance is not clear. In addition, the results of these trials have not been consistently demonstrated in other trials, particularly in trials with lansoprazole and pantoprazole.[39,41,47,50,53,55] Of note, most trials comparing esomeprazole to omeprazole utilized a dose of 40 mg for esomeprazole and 20 mg for omeprazole.[30,32,46,48] Since esomeprazole is a stereoisomer of omeprazole, comparing 40 mg of esomeprazole to 20 mg of omeprazole is comparable to evaluating a double dose of omeprazole.[30] Lightdale et al reported comparable healing rates and symptom relief in patients with erosive esophagitis treated with 20 mg daily of esomeprazole or omeprazole.[50] A 2007 Cochrane review concluded that there was no major difference in efficacy among the currently available PPIs for the short-term management of reflux esophagitis when administered in equivalent dosages.[87]

To date, head-to-head studies comparing dexlansoprazole to other PPIs are limited. Dexlansoprazole has consistently been shown to significantly improve control of heartburn symptoms, nighttime heartburn symptoms, and healing of erosive esophagitis compared to placebo.[33-35] The healing of erosive esophagitis indication was based upon two eight week, double-blind, international, controlled trials comparing dexlansoprazole 60 and 90 mg and lansoprazole 30 mg. The pooled results of these trials demonstrated that dexlansoprazole was noninferior to lansoprazole as 86% of patients receiving dexlansoprazole 60 mg once daily (N=1,296) and 88% of patients receiving 90 mg once daily (N=1,286) had healing of erosive esophagitis compared to 82% of patients receiving lansoprazole 30 mg once daily (P<0.05 for both dexlansoprazole groups vs lansoprazole). Relief of heartburn symptoms occurred at endpoint compared to baseline across all treatment groups; however, no significant between-group differences were observed.[38]

A randomized, double-blind, multicenter, placebo-controlled trial evaluating the maintenance of healed erosive esophagitis concluded that after six months of therapy both 60 and 90 mg of dexlansoprazole administered once daily demonstrated significantly higher erosive esophagitis maintenance (66.4 and 64.5%, respectively) compared to placebo (14.3%; P<0.00001 for both group comparisons) based upon crude rate analyses.[35] A similarly designed trial evaluated the maintenance of healed erosive esophagitis and heartburn symptom relief after receiving dexlansoprazole 30 or 60 mg or placebo for six months. The maintenance rate, according to crude rate analysis, for both 30 and 60 mg of dexlansoprazole was 66.4% at endpoint compared to 14.3% for placebo (P<0.00001). Moreover, the median percentage of 24-hour heartburn-free days was significantly greater for the dexlansoprazole 30 and 60 mg treatment arms compared to placebo (96, 91 and 29%, respectively; P<0.0025).[36]

In a trial evaluating the safety and efficacy of dexlansoprazole 30 and 60 mg once-daily compared to placebo in patients with non-erosive esophagitis and normal endoscopy screening, dexlansoprazole 30 and 60 mg therapy resulted in a significantly greater median percentage of days without day and nighttime symptoms compared to placebo therapy (54.9, 50.5 and 18.5%, respectively; P<0.00001). There was no statistically significant difference observed between the two active treatment groups. In addition, the median percentage of nights without heartburn symptoms favored the dexlansoprazole 30 and 60 mg groups compared to placebo (80.8, 76.9 and 51.7%, respectively; P<0.00001). Active treatment resulted in symptom improvement within three days of therapy compared to placebo and was maintained for the four week study duration.[37]

Meta-analyses and head-to-head trials comparing PPIs for the treatment of peptic ulcer disease with *Helicobacter pylori* have shown comparable rates of eradication when paired with comparable antibiotic regimens.[67-71,73-75,78] One small trial reported higher eradication rates for patients treated with esomeprazole than pantoprazole.[72] In a recent meta-analysis by McNicholl et al, both esomeprazole- and

rabeprazole-based *H pylori* regimens were considered more effective with regard to eradication rate compared to traditional PPIs (lansoprazole, omeprazole and pantoprazole).[77]

Nelson et al conducted an analysis of the impact of converting patients with GERD from omeprazole to lansoprazole through a managed care plan policy change.[86] Patients converted were surveyed by telephone prior to the interchange and 30 days after the interchange. One hundred and five patients completed both interviews. After the interchange, increased frequency of heartburn while awake was reported in 37% of the patients, 9% reported increased frequency of heartburn that kept them from falling asleep, 33% reported increased frequency of use of any over-the-counter heartburn preparations and 13% reported increased frequency of diet change due to heartburn symptoms (*P* values not reported). Mean patient satisfaction scores based on a 10-point scale (1 being not satisfied and 10 being completely satisfied) decreased significantly from baseline (9.0 vs 7.2; $P<0.001$). Cote et al evaluated whether patients with GERD who were previously managed on lansoprazole 30 mg twice daily could be maintained on rabeprazole 20 mg once daily after a formulary change at a Veterans' Affairs hospital.[89] Of 435 patients who had received lansoprazole 30 mg twice daily for at least 12 months, data was evaluated for 223 patients. Of these patients, 111 (50%) were successfully maintained on rabeprazole 20 mg once daily, 23 (10%) were able to discontinue PPI therapy and 89 (40%) were considered treatment failures (subsequent increase in PPI dose or a switch of PPI). Of these, 82 patients had recurrent GERD symptoms while on rabeprazole 20 mg once daily (of note, data for about half of the patients was excluded for reasons such as no documentation of GERD in the medical record, recent diagnosis of peptic ulcer, lack of follow-up and never received once daily PPI).

Meineche-Schmidt conducted a study in 829 patients investigating the long-term effect of health-care consumption when double doses of omeprazole were utilized.[90] Patients with dyspeptic symptoms were randomized to receive omeprazole 40 or 20 mg or placebo every morning for two weeks. Patients were evaluated on symptom relief. In addition, relapse rates and health-care consumption after 12 months were recorded. Complete symptom relief was comparable between omeprazole 40 mg (66.4%) and omeprazole 20 mg (63.0%) but higher than placebo (34.9%; *P* value not reported). Relapse rates after 12 months were comparable between all treatment arms (67.7% for omeprazole 40 mg, 64.7% for omeprazole 20 mg and 63.3% for placebo). There was no difference between treatment arms in the number of contacts with the general practitioner, referrals to specialists, hospitals or use of dyspepsia medications (specific data not reported).

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gastroesophageal Reflux Disease				
van Pinxteren et al[29] PPI-based therapy (esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) vs H2RA-based therapy (cimetidine, famotidine, nizatidine and ranitidine) vs prokinetic-based therapy (cisapride, domperidone and metoclopramide)	SR RCTs reporting symptomatic outcome after short-term treatment for GERD with PPIs, H2RA or prokinetic agents in adult patients with endoscopy-negative reflux disease or in which no endoscopy was performed	32 trials Up to 12 weeks	Primary: Heartburn remission (defined <1 day per week with mild heartburn) Secondary: (Partial) symptom relief and quality of life	Primary In patients receiving empiric treatment of GERD, there was a higher rate of heartburn remission with PPIs compared to placebo (RR, 0.37; 95% CI, 0.32 to 0.44). Compared to placebo, H2RAs was associated with a significant increase in the rate of heartburn remission (RR, 0.77; 95% CI,0.60 to 0.99). Treatment with a prokinetic was more effective compared to treatment with placebo with regard to heartburn remission (RR, 0.86; 95% CI, 0.73 to 1.01). Treatment with PPIs was significantly more effective compared to treatment with H2RAs with regard to heartburn remission (RR, 0.66; 95% CI, 0.60 to 0.73) Similarly, there was a significantly higher risk of heartburn remission with PPI treatment compared to treatment with prokinetics (RR, 0.53; 95% CI, 0.32 to 0.87). In patients with endoscopy negative reflux disease, heartburn remission was greater with PPI treatment compared to placebo (RR, 0.73; 95% CI, 0.67 to 0.78). Similarly, H2RA therapy was associated with higher heartburn remission rates compared to treatment with placebo (RR, 0.84; 95% CI, 0.74 to 0.95). The RR for PPI treatment compared to H2RA treatment was 0.78 (95% CI, 0.62 to 0.97). Compared to prokinetic therapy, PPI therapy was more effective at achieving heartburn remission (RR, 0.72; 95% CI, 0.56 to 0.92). Secondary: In placebo controlled trials of empirically treated patients, H2RAs and prokinetics were associated with overall symptom improvement (RR, 0.72; 95% CI, 0.63 to 0.81 and RR, 0.71; 95% CI, 0.56 to 0.91). The RR for overall

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				improvement with a PPI compared to an H2RA was 0.29 (95% CI, 0.17 to 0.51). Compared to placebo, H2RAs were more effective in daytime heartburn relief (RR, 0.80; 95% CI, 0.71 to 0.89) as were prokinetics (RR, 0.63; 95% CI, 0.51 to 0.77). No difference was reported between the two active treatments (RR, 0.83; 95% CI, 0.30 to 2.29). No evaluation was made for PPIs. Compared to placebo, improvement in nighttime heartburn relief was 0.80 with the H2RAs (95% CI, 0.71 to 0.89) and 0.63 (95% CI, 0.51 to 0.77) with the the prokinetic agents. No differences were reported between the treatments, and no comparison with PPIs was made. In those with endoscopy-negative reflux disease, heartburn remission was higher with PPIs (RR, 0.73; 95%CI, 0.67 to 0.78) and H2RAs (RR, 0.84; 95% CI, 0.74 to 0.95) compared to placebo. Treatment with PPIs was associated in an increased risk of heartburn remission in endoscopy negative patients compared to H2RA treatment (RR, 0.78; 95% CI, 0.62 to 0.97). Similarly PPI treatment was more effective compared to prokinetic treatment in this patient population (RR, 0.72; 95% CI, 0.56 to 0.92). Overall symptom improvement was achieved with PPI treatment (RR, 0.61; 95% CI, 0.54 to 0.69) and H2RA treatment (RR, 0.41; 95% CI, 0.13 to 1.33) compared to placebo treatment. Furthermore, PPI therapy was favored over treatment with an H2RA (RR, 0.41; 95% CI, 0.13 to 1.33). There was no significant difference between omeprazole 20 mg daily, omeprazole 10 mg daily and cisapride 10 mg four times daily with regard to the change in global PGWB and GSRS. There was a statistically significant improvement in the reflux dimension of the GSRS with PPI treatment compared to H2RA treatment ($P<0.05$). In one trial, the total GSRS at week four was significantly improved with omeprazole 20 mg compared to ranitidine 150 mg ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Klok et al[30] Direct comparison of short-term PPI therapy under the same clinical conditions	MA RCTs of PPI use in GERD, PUD or *H pylori* eradication	41 trials Duration varied	Primary: Success rates (defined as endoscopically determined cure for GERD and PUD or absence of *H pylori*) Secondary: Not reported	Primary: Comparisons between PPI treatments for GERD included the following: esomeprazole 40 mg/day compared to omeprazole 20 mg/day; esomeprazole 20 mg/day compared to omeprazole 20 mg/day; lansoprazole 30 mg/day compared to omeprazole 20 mg/day; lansoprazole 30 mg/day compared to omeprazole 40 mg/day; lansoprazole 15 mg/day compared to omeprazole 20 mg/day; lansoprazole 30 mg/day compared to pantoprazole 40 mg/day; pantoprazole 40 mg/day compared to omeprazole 20 mg/day; pantoprazole 20 mg/day compared to omeprazole 20 mg/day; rabeprazole 20 mg/day compared to omeprazole 20 mg/day and rabeprazole 10 mg/day compared to omeprazole 20 mg/day. For GERD treatment, one statistically significant difference was noted. After four weeks of treatment, esomeprazole 40 mg/day was associated with a significantly greater healing rate compared to omeprazole 20 mg/day (RR, 1.18; 95% CI, 1.14 to 1.23). For all other comparisons in GERD, no significant difference was reported. Comparisons between PPI treatments for ulcer healing included the following: esomeprazole 40 mg/day compared to omeprazole 20 mg/day; lansoprazole 30 mg/day compared to omeprazole 20 mg/day; pantoprazole 40 mg/day compared to omeprazole 20 mg/day; rabeprazole 20 mg/day compared to omeprazole 20 mg/day. For PUD treatment, one statistically significant difference was noted. After four weeks of treatment, pantoprazole 40 mg/day was associated with a significantly greater healing rate compared to omeprazole 20 mg/day (RR, 1.07; 95% CI, 1.02 to 1.13). For all other comparisons, no significant difference was reported. No significant differences were reported in *H pylori* eradication rates between PPIs. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Caro et al[31] Omeprazole, ranitidine or placebo vs lansoprazole, pantoprazole or rabeprazole	MA RCTs for GERD acute and maintenance therapy (placebo arm included)	41 trials Duration varied	Primary: Healing and relapse rates Secondary: Not reported	Primary: Compared to omeprazole 20 mg/day, the healing rate ratios after eight weeks were as follows: lansoprazole 30 mg/day healing rate ratios, 1.02 (95% CI, 0.98 to 1.06); rabeprazole 20 mg/day healing rate ratios, 0.93 (95% CI, 0.87 to 1.00) and pantoprazole 40 mg/day healing rate ratios, 0.98 (95% CI, 0.90 to 1.07). Relapse rates after six months were 6 to 29% with lansoprazole 30 mg/day, 9% with rabeprazole 20 mg/day and 7 to 42% with omeprazole 20 mg/day. No maintenance trials with pantoprazole were included. Secondary: Not reported
Edwards et al[32] Omeprazole 20 mg/day vs esomeprazole 40 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day or rabeprazole 20 mg/day	MA RCTs comparing omeprazole to other PPIs for acute treatment for GERD	12 trials 4 to 8 weeks	Primary: Healing rates Secondary: Not reported	Primary; Compared to omeprazole 20 mg/day, esomeprazole 40 mg/day had significantly greater healing rates at week four (RR, 1.14; 95% CI, 1.10 to 1.18) and at week eight (RR, 1.08; 95% CI, 1.05 to 1.10). Compared to omeprazole 20 mg/day, there was no significant difference in healing rates at four or eight weeks with lansoprazole 30 mg/day, pantoprazole 40 mg/day and rabeprazole 20 mg/day. Secondary: Not reported
Fass et al[33] Dexlansoprazole 30 mg QD Patients were switched from twice-daily PPI therapy to receive dexlansoprazole once-daily and placebo once daily.	MC, NR, PC, SB Patients, ≥18 years of age with GERD who were receiving maintenance therapy with a stable dose of BID PPI for ≤1 year but >8 weeks and ≤4 or fewer occurrences of heartburn in the	N=178 6 weeks	Primary: Proportion of patients whose heartburn remained well controlled (symptoms occurred ≤1 per week over the last four weeks of the treatment period)	Primary: The proportion of subjects whose heartburn remained well controlled after switching from previous BID PPI to QD dexlansoprazole, was 88% (95% CI, 82.7 to 93.4). Secondary: Treatment with dexlansoprazole was associated with a statistically significant increase in PAGI-QOL total score for patients who were well controlled compared to patients whose heartburn was not well controlled (P<0.05). Specifically, PAGI-QOL scores for diet and food habits (P<0.001) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	previous four weeks		Secondary: Change from baseline in each subscale and the total score of the PAGI-QOL and PAGI-SYM questionnaires in patients whose heartburn remained well controlled on QD dexlansoprazole and safety	relationship (P<0.05) were significantly improved among patients treated with dexlansoprazole who were considered to be well controlled compared to those who had uncontrolled heartburn. There was no statistically significant improvement in PAGI-SYM total score at week six among patients who were well controlled and those who remained uncontrolled with dexlansoprazole therapy (P value not reported). Patients considered to be well controlled following dexlansoprazole treatment experienced statistically significant improvements in bloating (P<0.05) and heartburn/regurgitation (P<0.05) compared to patients considered to have uncontrolled heartburn despite dexlansoprazole therapy. Overall, 44% of patients switching to QD dexlansoprazole reported at least one treatment-emergent adverse events of which most we mild or moderate in severity. The most frequently reported adverse event was upper respiratory tract infection (7%).
Fass et al[34] Dexlansoprazole 30 mg QD vs placebo After a screening period of up to 21 days, all patients underwent an upper endoscopy within four days prior to randomization to exclude patients with esophageal erosions.	DB, MC, PC, PG, RCT Patients 18 to 66 years of age with moderate to severe or very severe nocturnal heartburn, GERD-related sleep disturbances and a normal esophageal mucosa upon screening endoscopy	N=305 4 weeks	Primary: Percentage of nights without heartburn over four weeks Secondary: Percentage of patients with relief of nocturnal heartburn over last seven days, percentage of patients with relief of GERD-related sleep disturbances over the last seven days of treatment,	Primary: The percentage of nights free of heartburn was significantly higher in patients treated with dexlansoprazole compared to those receiving placebo (73.1 vs 35.7%; P<0.001). Secondary: The increase in heartburn-free nights for patients with mild-to-moderate, moderate-to-severe and severe-to-very severe was 30.2, 32.1 and 65.6%, respectively. A significantly higher percentage of patients experienced relief of nocturnal heartburn in the seven days following dexlansoprazole treatment compared to placebo (47.5 vs 19.6%; P<0.001). Dexlansoprazole treatment was associated with a significantly higher percentage of patients with relief of GERD-related symptoms in the previous seven days compared to patients treated with placebo (69.7 vs 47.9%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			mean severity of nocturnal heartburn during treatment, percentage of nights with GERD-related sleep disturbances, percentage of nights with each type of sleep disturbance, percentage of heartburn-free days, change from baseline to week four in PSQI, N-GSSIQ, and WPAI scores	During treatment, patients receiving dexlansoprazole had significantly lower scores for nocturnal heartburn severity compared to patients in the placebo group (0.48 vs 1.15; respectively; *P*<0.001). Patients receiving dexlansoprazole reported a significantly lower percentage of nights with sleep disturbance due to GERD symptoms compared to the placebo group (11.1 vs 36.8%; *P*<0.001). Treatment with dexlansoprazole was associated with significantly less GERD-related sleep disturbances for all types of disturbances compared to placebo (*P*<0.001), except for "sleep disturbances for other reasons" (*P*=0.377). Patients in the dexlansoprazole group experienced significant improvement in N-GSSIQ total score (*P*<0.001), the Nocturnal GERD Symptom Severity subscale (*P*<0.001), Morning Impact of Nocturnal GERD (*P*<0.001), Concern about Nocturnal GERD (*P*<0.001) and WPAI for work production (*P*=0.036).
Howden et al[35] Dexlansoprazole 60 mg QD vs dexlansoprazole 90 mg QD vs placebo Antacid use was permitted as rescue medication.	DB, MC, RCT Patients aged ≥18 years who had participated in one of two previous erosive esophagitis healing trials and had endoscopically proven healed erosive esophagitis	N=451 6 months	Primary: Maintenance of healed erosive esophagitis Secondary: Percentage of days and nights without heartburn, heartburn and GERD symptom severity (scale of 0=none to 4=very severe), percentage of days without rescue medication	Primary: The maintenance rates of healed erosive esophagitis were significantly higher with dexlansoprazole therapy (86.6 and 82.1% with 60 and 90 mg respectively) compared to placebo (25.7%; *P*<0.00001). Secondary: The median days without heartburn were 95.8 and 94.4% for 60 and 90 mg dexlansoprazole, respectively compared to 19.2% with placebo (*P*<0.00001 for both) and the median heartburn-free nights were 98.3, 97.1 and 50.0%, respectively (*P*<0.00001 for both). The mean heartburn severity scores were 0.03 with dexlansoprazole 60 mg, 0.04 with dexlansoprazole 90 mg and 1.00 with placebo (*P*<0.00001 for both). Median days without rescue medication were 94.9, 93.6 and 27.5% (*P*<0.00001 for both). Diarrhea, flatulence, gastritis and abdominal pain were the most frequently reported adverse events noted with dexlansoprazole therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and adverse events	
Metz et al[36] Dexlansoprazole 30 mg QD vs dexlansoprazole 60 mg QD vs placebo Antacid use was permitted as rescue medication.	DB, MC, RCT Patients aged ≥18 years who had participated in one of two erosive esophagitis healing trials and had endoscopically proven healed erosive esophagitis	N=445 6 months	Primary: Maintenance of healed erosive esophagitis Secondary: Percentage of days and nights without heartburn, heartburn and GERD symptom severity (scale of 0=none to 4=very severe), percentage of days without rescue medication and adverse events	Primary: After six months, healing was maintained in 66.4, 66.4 and 27.2% of dexlansoprazole 30 mg, 60 mg and placebo patients, respectively (*P*<0.00001). Secondary: Twenty-four hour heartburn-free days were detected in significantly more patients on active treatment than placebo (96, 91 and 29% of dexlansoprazole 30 mg, 60 mg and placebo patients, respectively; *P*<0.0025). Nights without heartburn were significantly greater with active treatment compared to placebo with 99% of the dexlansoprazole 30 mg group, 96% of the dexlansoprazole 60 mg group and 72% of the placebo group reportedly heartburn-free at night (*P*<0.0025). In addition, severity of symptoms was significantly lower with dexlansoprazole therapy (data not reported). Ninety-eight, 96 and 44% of dexlansoprazole 30 mg, 60 mg and placebo patients, respectively did not require rescue medication. Upper respiratory infection, diarrhea, and joint-related symptoms were reported significantly more often with dexlansoprazole therapy compared to placebo.
Fass et al[37] Dexlansoprazole 30 mg QD vs dexlansoprazole 60 mg QD vs placebo	DB, MC, RCT Patients aged ≥18 years with non-erosive esophagitis and normal endoscopy screening	N=947 4 weeks	Primary: Percentage of 24-hour heartburn-free days Secondary: Nights without heartburn, severity of heartburn (scale of 0=none to 4=very severe), days without rescue medication and adverse	Primary: All outcomes significantly favored active treatment over placebo. The median rate of 24-hour heartburn free days was 54.9% in the dexlansoprazole 30 mg group and 50.0% in the dexlansoprazole 60 mg group compared to 18.5% in the placebo group (*P*<0.00001). Secondary: The median percentage of nights without heartburn symptoms was 80.8, 76.9 and 51.7% for dexlansoprazole 30 mg, 60 mg and placebo, respectively (*P*<0.00001 for both compared to placebo). The mean severity score of daytime/nighttime heartburn was 0.66, 0.69 and 1.04, respectively (*P*<0.00001 for both compared to placebo). The median percentage of days without rescue medication was 63.0% for both dose of dexlansoprazole compared to 37.3% with placebo (*P*<0.00001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Antacid use was permitted as rescue medication.			events	The most frequently reported adverse events included diarrhea, headache, nausea, and vomiting.
Sharma et al[38] Dexlansoprazole 60 mg QD vs dexlansoprazole 90 mg QD vs lansoprazole 30 mg QD Antacid use was permitted as rescue medication.	2 DB, MC, RCT Patients ≥18 years of age with endoscopically confirmed erosive esophagitis	N=4,092 8 weeks	Primary: Complete healing of erosive esophagitis over eight weeks Secondary: Complete healing of erosive esophagitis at four weeks, complete healing of grade C or D erosive esophagitis over eight weeks, percentage of days and nights without heartburn, heartburn and GERD symptom severity, percentage days without rescue medication and adverse events	Primary: Dexlansoprazole therapy was determined to be NI to lansoprazole in complete healing of erosive esophagitis over eight weeks with pooled results from both trials showing 86% of dexlansoprazole 60 mg patients, 88% of dexlansoprazole 90 mg patients and 82% of lansoprazole patients experiencing complete healing (P<0.05). Secondary: Complete healing of erosive esophagitis at week four was >64% in all treatment groups (P values not reported). Complete healing of grade C or D erosive esophagitis was detected in 79, 80 and 72% of dexlansoprazole 60 mg, 90 mg and lansoprazole patients, respectively. Only the difference between dexlansoprazole 90 mg and lansoprazole reached statistical significance (P<0.05). No significant differences were detected among the three groups in percentage of days and nights without heartburn, heartburn and GERD symptom severity and percentage of days without rescue medication (specific data not reported). The most frequently reported adverse events, which were similar among groups, included diarrhea, nausea and vomiting, gastrointestinal and abdominal pain, headache and upper respiratory infection.
Chey et al[39] Esomeprazole 40 mg QD vs lansoprazole 30 mg QD	DB, MC, RCT Adult patients with symptomatic GERD	N=3,034 2 weeks	Primary: Average symptom severity after day three Secondary: Percentage of patients without	Primary: No statistically significant differences were noted between the two treatment groups in symptom severity after day three (P value not reported). Secondary: No statistically significant differences were noted for any of the secondary endpoints (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			daytime and nighttime heartburn after day one and symptom relief after day one and symptom severity after day one, seven and 14	
Castell et al[40] Esomeprazole 40 mg QD in the morning vs lansoprazole 30 mg QD in the morning	DB, MC, PG, RCT Adults with endoscopically documented erosive esophagitis; patients were excluded if they had gastrointestinal bleeding, history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders or strictures, Barrett's esophagitis, upper gastrointestinal malignancy or other severe concomitant disease	N=5,241 8 weeks	Primary: Healing rates at eight weeks Secondary: Healing rates at week four, resolution of investigator-recorded heartburn at week four, time to first and time to sustained relief of heartburn and proportion of heartburn-free days and nights	Primary: Esomeprazole demonstrated significantly higher healing rates at eight weeks compared to lansoprazole (92.6 vs 88.8%; *P*=0.0001). Secondary: Esomeprazole demonstrated higher healing rates at four weeks compared to lansoprazole (79.4 vs 75.1%; *P* value not reported). Resolution of heartburn at week four was significantly higher with esomeprazole compared to lansoprazole (62.9 vs 60.2%; *P*≤0.05). No significant difference was observed in time to first resolution of heartburn (median of two days for both treatment groups); however, time to sustained relief was significantly less with esomeprazole (seven vs eight days; *P*≤0.01). There was no significant difference in the proportion of heartburn-free days between treatment groups; however, heartburn-free nights were significantly higher with esomeprazole (87.1 vs 85.8%; *P*≤0.05).
Howden et al[41] Esomeprazole 40 mg QD vs lansoprazole 30 mg QD	DB, MC, RCT Adult patients with endoscopically documented erosive esophagitis	N=284 8 weeks	Primary: Healing rates at eight weeks Secondary: Healing rates at week four, proportion of	Primary: Comparable healing rates at week eight were observed between esomeprazole and lansoprazole (89.1 vs 91.4%, respectively; *P* value not reported). Secondary: Healing rates at week four were comparable between the two treatment groups (77.0% for lansoprazole and 78.3% for esomeprazole; *P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			patients reporting heartburn-free days and nights, and rate of healing or improvement of esophagitis by two grades	reported). The percentage of patients reporting heartburn-free days and nights was comparable between treatment groups. Healing or improvement of esophagitis by two grades was observed in 90.0% of patients taking lansoprazole and 81.0% taking esomeprazole.
Devault et al[42] Esomeprazole 20 mg QD vs lansoprazole 15 mg QD	DB, MC, PG, RCT Patients 18 to 75 years of age with erosive esophagitis (Los Angeles grades A, B, C or D) who were treated and healed; patients were excluded if they had other gastrointestinal complications, bleeding disorders or other diseases or conditions that could affect study participation	N=1,026 6 months	Primary: Remission rates (defined as no detectable erosive esophagitis and no study discontinuation due to reflux symptoms) at six months Secondary: Observed remission rate at three months and six months	Primary: Estimated endoscopic/symptomatic remission rate during a period of six months was significantly higher (*P*=0.0007) for patients on esomeprazole (84.8%) compared to lansoprazole (75.9%). Secondary: Observed endoscopic/symptomatic remission rates at three months (92.8 vs 86.8%; *P*<0.0001) and six months (86.2 vs 77.6%; *P*<0.0001) were significantly higher in the esomeprazole group compared to the lansoprazole group. There was no significant difference between esomeprazole and lansoprazole at six months with regard to patients reporting no heartburn (82.9 and 79.2%), acid regurgitation (86.8 and 85.8%), dysphagia (97.6 and 96.4%) or epigastric pain (91.6 and 89.5%). Both treatments were well tolerated.
Fennerty et al[43] Esomeprazole 40 mg QD vs lansoprazole 30 mg QD	DB, MC, RCT Patients with moderate-severe erosive esophagitis (Los Angeles Grade C or D); patients were excluded if they had gastrointestinal bleeding, history of gastric or esophageal surgery, Zollinger-	N=999 8 weeks	Primary: Healing rates at week eight Secondary: Resolution of heartburn symptoms at week four	Primary: Healing rates at week eight were significantly greater in patients taking esomeprazole compared to lansoprazole (82.4 vs 77.5%; *P*=0.007). Secondary: Significantly more patients taking esomeprazole had resolution of heartburn symptoms at week four compared to lansoprazole (72.0 vs 63.6%; *P*=0.005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	Ellison syndrome, esophageal motility disorders, inflammatory bowel disease, esophageal stricture, Barrett's esophagitis, duodenal or gastric ulcer, upper gastrointestinal malignancy or other severe concomitant disease			
Lauritsen et al[44] Esomeprazole 20 mg QD vs lansoprazole 15 mg QD	DB, MC, RCT Patients with healed esophagitis; patients were excluded if they had gastrointestinal bleeding, history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders, inflammatory bowel disease, esophageal stricture, Barrett's esophagitis, duodenal or gastric ulcer, upper gastrointestinal malignancy or other severe concomitant disease	N=1,391 6 months	Primary: Remission rates at six months Secondary: Not reported	Primary: Remission rates at six months were significantly higher with esomeprazole compared to lansoprazole (83 vs 74%; *P*<0.0001). Secondary: Not reported
Tsai et al[45] Esomeprazole 20 mg	MC, PG, RCT, SB Patients 18 to 80 years	N=622 6 months	Primary: Time to discontinuation	Primary: Time to discontinuation from maintenance phase due to unwillingness to continue was significantly longer for patients taking esomeprazole on demand

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
on-demand therapy vs lansoprazole 15 mg QD All patients received esomeprazole 20 mg QD for two to four weeks for acute treatment of GERD and were then randomized into the above treatment groups.	of age with a >6 month history of GERD without esophageal mucosal breaks and reported symptoms in >4 out of the previous seven days; patients were excluded if they received >10 days of PPI therapy in the previous 28 days, were on anticholinergics, cisapride, prostaglandin analogues, NSAIDs or salicylates		from maintenance phase due to unwillingness to continue Secondary: Time to discontinuation due to insufficient heartburn control, patient satisfaction and symptom assessment	compared to lansoprazole (*P*=0.001). At six months, significantly more patients on lansoprazole were unwilling to continue therapy compared to esomeprazole (13 vs 6%; *P*=0.001). Secondary: Of the patients discontinuing therapy, 4.8% taking lansoprazole and 2.9% taking esomeprazole reported heartburn as the reason for unwillingness to continue (*P* value not reported). The time to discontinuation due to insufficient heartburn control was not reported. Significantly more patients cited adverse events with lansoprazole as the reason for unwillingness to continue treatment (*P*=0.0028). Patient satisfaction was significantly higher with esomeprazole after one month of treatment (*P*=0.02). At three and six months, patient satisfaction was similar for both groups. The frequency of heartburn symptoms recorded at clinic visits was higher with esomeprazole compared to lansoprazole at one, three and six months (*P* value not reported).
Richter et al[46] Esomeprazole 40 mg QD vs omeprazole 20 mg QD	DB, MC, PG, RCT Adult patients with erosive esophagitis; patients were excluded if they tested positive for *H pylori*, had gastrointestinal bleeding, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal motility disorders, esophageal stricture, Barrett's esophagitis, duodenal or gastric ulcer,	N=2,425 8 weeks	Primary: Healing rates at eight weeks Secondary: Healing rates at four weeks, and resolution of heartburn symptoms at week four, time to first resolution and sustained resolution of heartburn and proportion of heartburn-free	Primary: Significantly more patients taking esomeprazole were healed at eight weeks compared to those taking omeprazole (93.7 vs 84.2%; *P*<0.001). Secondary: Significantly more patients taking esomeprazole were healed at four weeks compared to those taking omeprazole (81.7 vs 68.7%; *P*<0.001). Significantly more patients taking esomeprazole had complete resolution of heartburn compared to those taking omeprazole (68.3 vs 58.1%; *P*<0.001). Time to first resolution was significantly greater with esomeprazole at day one (45.3 vs 32.0%; *P*≤0.0005) and day seven (85.6 vs 81.6%; *P*≤0.0005) compared to omeprazole. Time to sustained resolution with esomeprazole was significantly greater at day one, 14, and 28 compared to omeprazole (*P*≤0.0005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	inflammatory bowel disease, upper gastrointestinal malignancy, unstable diabetes or other severe disease		days and nights	Esomeprazole resulted in greater heartburn-free days (74.9 vs 69.7%) and nights (90.8 vs 87.9%; both *P*<0.001).
Armstrong et al[47] Esomeprazole 40 mg QD vs esomeprazole 20 mg QD vs omeprazole 20 mg QD In study A, patients received either esomeprazole 40 mg QD, esomeprazole 20 mg QD, or omeprazole 20 mg QD. In study B, patients received esomeprazole 40 mg QD or omeprazole 20 mg QD. In study C, patients received esomeprazole 20 mg QD or omeprazole 20 mg QD.	3 DB, MC, PG, RCTs Patients with heartburn for >6 months with a normal endoscopy were included in one of three trials	N=2,645 4 weeks	Primary: Complete resolution of heartburn at four weeks Secondary: Complete resolution of heartburn at 14 days, adequate control of heartburn, relief of other reflux and gastrointestinal symptoms and relief of heartburn (assessed by patient diary)	Primary: Complete resolution of heartburn at four weeks was comparable for all treatment arms throughout the three studies. Secondary: Complete resolution of heartburn at two weeks was comparable for all treatment arms throughout the three studies. For adequate control of heartburn in study A, 60.5% on esomeprazole 40 mg, 66.0% on esomeprazole 20 mg and 63.1% on omeprazole 20 mg reported adequate control (*P* value not reported). In study B, 73.5% taking esomeprazole 40 mg and 72.8% on omeprazole 20 mg reported adequate heartburn control (*P* value not reported). In study C, 67.9% taking esomeprazole 20 mg and 65.3% on omeprazole 20 mg reported adequate heartburn control (*P* value not reported). After four weeks, relief of other reflux and gastrointestinal symptoms was comparable in all treatment arms throughout the three studies. In study A, relief of heartburn reported by patients was higher with esomeprazole 20 mg (*P* value not reported). No differences were detected throughout the other two studies.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kahrilas et al[48] Esomeprazole 40 mg QD vs esomeprazole 20 mg QD vs omeprazole 20 mg QD	DB, MC, PG, RCT Patients with endoscopically documented reflux esophagitis; patients were excluded if they had gastrointestinal bleeding, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal motility disorders, esophageal stricture, Barrett's esophagitis, upper gastrointestinal malignancy or other severe concomitant disease	N=1,960 8 weeks	Primary: Healing rates after eight weeks Secondary: Resolution of heartburn symptoms at week four, time to first and time to sustained relief of heartburn and proportion of heartburn-free days and nights	Primary: Healing rates for both esomeprazole 40 mg (94.1%; *P*<0.001 compared to omeprazole) and 20 mg (89.9%; *P*<0.05 compared to omeprazole) were statistically higher than omeprazole 20 mg (86.9%). Secondary: Resolution of heartburn symptoms was significantly higher for patients taking esomeprazole 40 mg compared to those taking omeprazole (64.7 vs 57.2%; *P*=0.005). There were no significant differences between omeprazole and esomeprazole 20 mg (61.0%). Time to first resolution of heartburn symptoms was significantly higher for patients taking esomeprazole 40 mg compared to omeprazole (*P*=0.013). There were no significant differences between omeprazole and esomeprazole 20 mg. Time to sustained resolution of heartburn symptoms was significantly higher for patients taking esomeprazole 40 mg (five days) compared to omeprazole (nine days; *P*=0.0006). There were no statistically significant differences between omeprazole and esomeprazole 20 mg (eight days). Proportion of heartburn-free days was significantly higher for patients taking esomeprazole 40 mg (72.7%) compared to omeprazole (67.1%; *P*=0.002). There were no significant differences between omeprazole and esomeprazole 20 mg (69.3%). Proportion of heartburn-free nights was significantly higher for patients taking esomeprazole 40 mg (84.7%; *P*=0.001) and 20 mg (83.6%; *P*=0.013) compared to omeprazole (80.1%).
Schmitt et al[49] Esomeprazole 40 mg QD vs	DB, MC, PG, RCT Patients 18 to 75 years old with erosive esophagitis confirmed by endoscopy; patients were excluded if	N=1,148 8 weeks	Primary: Proportion of patients with healed erosive esophagitis at week eight	Primary: The proportion of patients with healed erosive esophagitis at week eight was 92.2% for esomeprazole and 89.9% for omeprazole (*P*=0.189). The proportion of patients with healed erosive esophagitis at week four was 71.5% for esomeprazole and 68.6% for omeprazole (no *P* value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
omeprazole 20 mg QD	positive for *H pylori*, any bleeding disorder, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal strictures or Barrett's esophagus		Secondary: Diary and investigator assessments of heartburn symptoms and safety	Treatment with esomeprazole was associated with significantly higher healing rates compared to omeprazole at weeks eight (88.4 vs 77.5%; *P*=0.007) and four (60.8 vs 47.9%; *P*=0.02) in patients with moderate-to-severe (Los Angeles grade C or D) erosive esophagitis at baseline but were not significantly different for patients with mild disease (grade A or B). Secondary: After four weeks of treatment, there were no significant differences between esomeprazole and omeprazole in the proportions of patients with investigator-assessed resolution of heartburn (65.0 vs 63.1%; *P*=0.48), the percentage of heartburn-free days (74.5 vs 73.0%; *P*=0.39) or the percentage of heartburn-free nights (86.2 vs 84.5%; *P*=0.21). Both treatments had similar tolerability.
Lightdale et al[50] Esomeprazole 20 mg QD vs omeprazole 20 mg QD	DB, MC, PG, RCT Patients 18 to 75 years old with erosive esophagitis confirmed by endoscopy; patients excluded if positive for *H pylori*, any bleeding disorder, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal strictures or Barrett's esophagus	N=1,176 8 weeks	Primary: Proportion of patients with healed erosive esophagitis at weeks eight Secondary: Diary and investigator assessments of heartburn symptoms and safety	Primary: The proportion of patients with healed erosive esophagitis at week eight was 90.6% for esomeprazole and 88.3% for omeprazole (*P*=0.621). Similar healing rates were achieved at weeks four and eight with esomeprazole and omeprazole in the entire study population and when patients were classified according to baseline erosive esophagitis severity. Secondary: Patients in both treatment groups had similar control of heartburn at week four. Adverse events were reported with similar frequencies among the esomeprazole and omeprazole patients.
Labenz et al[51] (Treatment) Esomeprazole 40 mg QD vs	DB, MC, RCT Adult patients with erosive esophagitis confirmed by endoscopy; patients were excluded if they had peptic ulcers,	N=3,170 8 weeks	Primary: Healing rates at eight weeks Secondary: Healing rates at four and eight weeks by baseline	Primary: At eight weeks, healing rates for esomeprazole (95.5%) were significantly higher compared to pantoprazole (92.0%; *P*<0.001). Secondary: At four and eight weeks, healing rates for esomeprazole were significantly higher compared to pantoprazole for erosive esophagitis grades B to D (Los Angeles grading; *P*<0.05). No significant difference was noted for grade A

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pantoprazole 40 mg QD	Zollinger-Ellison syndrome, esophageal stricture or Barrett's esophagitis		esophagitis severity, time to sustained symptom relief and proportion of heartburn-free days	esophagitis. Time to sustained resolution of heartburn symptoms was significantly shorter with esomeprazole (six days) compared to pantoprazole (eight days; *P*<0.001). Proportion of heartburn-free days was significantly higher with esomeprazole (70.7%) compared to omeprazole (67.3%; *P*<0.01).
Labenz et al[52] (Maintenance) Esomeprazole 20 mg QD vs pantoprazole 20 mg QD	DB, MC, RCT Patients from the EXPO Study with healed erosive esophagitis (confirmed by endoscopy at weeks four or eight) and free of moderate-to-severe heartburn and acid regurgitation for seven days prior to the maintenance study entry (see above EXPO Study)	N=2,766 6 months	Primary: Proportion of patients in endoscopic plus symptomatic remission Secondary: Relapse based on endoscopic findings	Primary: Following six months of treatment, the proportion of patients in endoscopic and symptomatic remission was significantly greater for those receiving esomeprazole (87.0%) compared to pantoprazole (74.9%; *P*<0.0001). Post hoc analyses showed that esomeprazole was significantly more effective than pantoprazole in patients with Los Angeles grades A, B and C but not grade D. Esomeprazole produced a higher proportion of patients free of moderate-to-severe GERD symptoms and fewer discontinuations because of symptoms than pantoprazole (92.2 vs 88.5%; *P*<0.001). Secondary: Following six months of treatment, esomeprazole was significantly more effective than pantoprazole for maintaining endoscopic healing of erosive esophagitis (88.1 vs 76.6%; *P*<0.0001).
Scholten et al[53] Esomeprazole 40 mg QD vs pantoprazole 40 mg QD	DB, MC, PG, RCT Adult patients with GERD grade B and C (Los Angeles classification system); patients excluded if they had peptic ulcers, Zollinger-Ellison syndrome, pyloric stenosis and esophageal and/or gastrointestinal surgery	N=217 4 weeks	Primary: Relief of GERD-related symptoms Secondary: Relief rates of GERD-related symptoms, gastrointestinal system rating scale score and time to first symptom relief	Primary: Both treatment groups reported similar relief of gastrointestinal symptoms (*P*>0.05). Secondary: At four weeks, the proportion of patients reporting no or mild heartburn was 99% with pantoprazole and 98% with esomeprazole. There were no significant differences in gastrointestinal system rating scale scores between the two treatment groups (*P*>0.05). Patients taking pantoprazole reported time to first symptom relief after a mean of 3.7 days compared to 5.9 days with esomeprazole (*P*=0.034).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Glatzel et al[54] Esomeprazole 40 mg QD for four weeks vs pantoprazole 40 mg QD for four weeks	DB, MC, PG, RCT Patients ≥18 years of age with endoscopically confirmed GERD grades A to D; patients were excluded if they had a gastric hypersecretory condition, previous gastrointestinal surgery, esophageal strictures, Barrett's esophagus, acute peptic ulcer or ulcer complications, pyloric stenosis or inflammatory bowel diseases	N=561 6 weeks	Primary: Compare GERD symptom course by means of a validated reflux questionnaire (ReQuest®), number of symptom episodes and rate of relapse Secondary: Safety	Primary: Pantoprazole was shown to be as effective as esomeprazole based on mean ReQuest® score that evaluated gastrointestinal symptoms. During the posttreatment period, the proportion of patients experiencing a symptomatic relapse (51 vs 61%; *P*=0.0216) and the number of symptom episodes (0.56 vs 0.74; *P*=0.0095) were significantly lower in patients on pantoprazole than on esomeprazole. Secondary: In general, both therapies were well tolerated and there was no significant difference in adverse events between the two groups.
Goh et al[55] EMANCIPATE Esomeprazole 20 mg QD vs pantoprazole 20 mg QD	DB, MC, PG, RCT Patients ≥18 years of age with endoscopically confirmed GERD who received four to eight weeks of pantoprazole 40 mg QD and were healed; patients were excluded if they had Zollinger-Ellison syndrome or other gastric hypersecretory condition, pyloric stenosis, acute peptic	N=1,303 6 months	Primary: Difference between combined endoscopic and symptomatic remission rates Secondary: Safety	Primary: Esomeprazole and pantoprazole were equally effective in maintaining patients in remission. In the ITT analysis, 85% of esomeprazole and 84% of pantoprazole patients remained in combined endoscopic and symptomatic remission at six months. Secondary: Both treatments were well tolerated and safe.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	ulcer and ulcer complications, endoscopically negative symptomatic GERD, esophageal strictures, Barrett's esophagus or pregnant or nursing			
Sharma et al[56] Lansoprazole 30 mg QD vs omeprazole 20 mg QD	MA RCTs of patients with endoscopically diagnosed erosive esophagitis where healing rates had to be reported after four and/or eight weeks	6 trials 4 to 8 weeks	Primary: Differences in pooled healing rates at four and eight weeks/ protocol and ITT data Secondary: Not reported	Primary: Pooled healing rates after four weeks were 77.7% for lansoprazole and 74.7% for omeprazole (absolute benefit increase, 3.1%; 95% CI, -1.1 to 7.3) in the per protocol analysis. After four weeks, pooled healing rates were 72.7% for lansoprazole and 70.8% for omeprazole (absolute benefit increase, 2.0%; 95% CI, -2.0 to 6.0) for the ITT analysis. After eight weeks, pooled healing rates were 88.7% for lansoprazole and 87.0% for omeprazole (absolute benefit increase, 1.7%; 95% CI, -1.5 to 5.0) in the per protocol analysis. After eight weeks, pooled healing rates were 83.3% for lansoprazole and 81.8% for omeprazole (absolute benefit increase, 1.5%; 95% CI, -1.9 to 4.9) in the ITT analysis. Lansoprazole and omeprazole healing rates were not statistically different. Secondary: Not reported
Richter et al[57] Lansoprazole 30 mg QD vs	DB, MC, RCT Adult patients with endoscopically documented erosive esophagitis; patients were excluded if they	N=3,510 8 weeks	Primary: Percentage of heartburn-free days and nights following one to three days and one week of	Primary: The percentage of heartburn-free days was significantly higher with lansoprazole compared to omeprazole after one to three days of treatment and after one week of treatment (P<0.0001). The percentage of heartburn-free nights was significantly higher with lansoprazole compared to omeprazole after one to three days of treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
omeprazole 20 mg QD	had gastrointestinal bleeding, history of gastric or esophageal surgery, esophageal motility disorders, esophageal stricture, or duodenal or gastric ulcers		treatment and the frequency and severity of day- and nighttime heartburn Secondary: Not reported	and after one week of treatment (*P*<0.0001). Average severity of heartburn symptoms was significantly less in patients taking lansoprazole compared to omeprazole. Significantly higher number of patients taking lansoprazole had recorded no heartburn compared to omeprazole at anytime during the first 14 days (*P*<0.001). At eight weeks, the number of patients reporting no heartburn throughout the entire study was significantly higher for lansoprazole (*P*<0.05). Secondary: Not reported
Pilotto et al[58] Lansoprazole 30 mg QD vs omeprazole 20 mg QD vs pantoprazole 40 mg QD vs rabeprazole 20 mg QD Patients who were *H pylori* positive were treated with the PPI and two antibiotics (amoxicillin, clarithromycin or	OL, RCT Patients >65 years of age with endoscopically diagnosed esophagitis; patients were excluded if history of Zollinger-Ellison syndrome, pyloric stenosis, previous surgery of the esophagus and/or gastrointestinal tract or gastrointestinal malignancy	N=320 8 weeks	Primary: Healing of esophagitis, gastrointestinal symptoms (e.g., heart burn, acid regurgitation, epigastric pain) and adverse events Secondary: Not reported	Primary: ITT healing rates of esophagitis were 85.0% for lansoprazole, 75.0% for omeprazole, 90.0% for pantoprazole (*P*=0.02 vs omeprazole) and 88.8% for rabeprazole (*P*=0.04 vs omeprazole). Dividing patients according to the grades of esophagitis, omeprazole was significantly less effective than the three other PPIs in healing grade I esophagitis (healing rates 81.8 vs 100, 100 and 100%, respectively; *P*=0.012). Healing rates were not significantly different for grades II (*P*=0.215) or III to IV (*P*=0.458) esophagitis. Pantoprazole and rabeprazole (100%) were more effective vs omeprazole (86.9%; *P*=0.0001) and lansoprazole (82.4%; *P*=0.0001) in decreasing heartburn. Omeprazole (100%), pantoprazole (92.2%) and rabeprazole (90.1%) were more effective compared to lansoprazole (75.0%; *P*<0.05) in decreasing acid regurgitation. Omeprazole (95.0%), pantoprazole (95.2%) and rabeprazole (100%) were more effective compared to lansoprazole (82.6%; *P*<0.05) in decreasing epigastric pain. All four PPIs were well tolerated and there was no statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metronidazole) for seven days.				difference in the prevalence of adverse events among the four treatment groups. Secondary: Not reported
Pouchain et al[59] Omeprazole 20 mg QD vs sodium alginate and sodium bicarbonate oral suspension 10 mL QID	AC, DB, DD, MC, NI, RCT Patients 18 to 60 years of age with two to six days of GERD episodes per week, with heartburn, with or without regurgitation, who were no taking alginate/ antacid or PPI in previous two months	N=241 14 days	Primary: Time to onset of the first 24-hour heartburn-free period Secondary: Mean number of days without heartburn at day seven, patient's overall qualitative self-assessment of pain relief on day seven (on five-point Likert scale) and pain intensity on day seven and day 14 (VAS) and adverse event	Primary: There was no statistically significant difference between the omeprazole and sodium alginate treatment groups with regard to the mean time to onset of the first 24-hours heartburn-free (2.0±2.2 vs 2.0±2.3; *P*=0.93). The mean intergroup difference was 0.01±1.55 days (95% CI, -0.41 to 0.43), which was less than the lower limit of the predetermined 95% CI (-0.5), thus demonstrating the NI of the two treatments. Secondary: The mean number of heartburn-free days at day seven was significantly greater for patients treated with omeprazole compared to sodium alginate and sodium bicarbonate (3.7±2.3 vs 3.1±2.1 days; *P*=0.02). At day seven, the overall self-assessed pain relief was significantly improved in the omeprazole group compared to sodium alginate and sodium bicarbonate (*P*=0.049). There was no statistically significant difference between patients receiving omeprazole or sodium alginate and sodium bicarbonate with regard to pain scores at day seven (*P*=0.11) or day 14 (*P*=0.08). At least one adverse event was reported in 14.2% of omeprazole-treated patients compared to 12.6% of patients receiving sodium alginate and sodium bicarbonate (*P*=0.70). No statistically significant differences in adverse events were reported at day seven (*P*=0.97) or day 14 (*P*=0.91). The most commonly reported adverse events were nausea (1.8%), constipation (1.5%), rhinopharyngitis (1.5%), drug intolerance (1.1%), abdominal pain, diarrhea, abdominal distension, rhinitis and cough (0.7% each).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bardhan et al[60] Omeprazole 20 mg QD vs pantoprazole 20 mg QD	OL, PG, RCT Adult patients with grade I GERD; patients were excluded if they had grade II, III or IV GERD, gastrointestinal bleeding, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal motility disorders, pyloric stenosis, esophageal stricture or duodenal or gastric ulcers	N=327 8 weeks	Primary: Rate of symptom relief at weeks two and four and healing rates at week four and eight Secondary: Not reported	Primary: At two and four weeks, the rate of symptom relief was similar for pantoprazole (70 and 77%) and omeprazole (79 and 84%; *P* value not reported). Healing rates at four weeks were comparable between pantoprazole (84%) and omeprazole (89%; *P* value not reported). Healing rates at eight weeks were comparable between pantoprazole (90%) and omeprazole (95%; *P* value not reported). Secondary: Not reported
Delcher et al[61] Omeprazole 20 mg QD vs rabeprazole 20 mg QD vs rabeprazole 10 mg BID	DB, PG, RCT Adult patients with ulcerative or erosive GERD; patients were excluded if they had grade I GERD, history of gastric or esophageal surgery, esophageal motility disorders or pyloric stenosis	N=310 8 weeks	Primary: Healing rates Secondary: Improvement of gastrointestinal symptoms, number of hours missed from normal daily activity, the use of antacids and physical well-being	Primary: At four weeks, the rates of healing were comparable among rabeprazole QD (94%), rabeprazole BID (93%) and omeprazole (98%; *P* value not reported). At four weeks, the rates of healing were comparable among rabeprazole QD (97%), rabeprazole BID (98%) and omeprazole (100%; *P* value not reported). Secondary: At four and eight weeks, improvements in gastrointestinal symptoms were comparable among all groups (*P* value not reported). Use of antacid tablets was comparable between all groups (*P* value not reported). There were no significant differences between groups in the General Well-Being Schedule (a quality-of-life measurement) or in a rating of overall physical well being.
Pace et al[62] Omeprazole 20 mg QD	DB, RCT Patients with grade I to	N=560 8 weeks	Primary: Healing rates	Primary: After eight weeks, rates of healing for rabeprazole (97.9%) were equivalent to omeprazole (97.5%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs rabeprazole 20 mg QD	III GERD		Secondary: Time to first day with satisfactory relief	Secondary: Rabeprazole had a statistically faster time to satisfactory relief (2.8 days) compared to omeprazole (4.7 days; *P*=0.0045).
Mönnikes et al[63] Pantoprazole 40 mg QD for 4 to 16 weeks (complete remission treatment group) vs pantoprazole 30 mg QD for four to eight weeks (classical treatment group)	DB, MC, PC, RCT Patients ≥18 years of age with endoscopically confirmed GERD (Los Angeles grades A, B, C or D)	N=626 16 weeks	Primary: Time to endoscopic relapse and/or unwillingness to continue due to GERD related symptoms within six months (after cessation of PPI treatment), adverse events Secondary: Not reported	Primary: There was no statistically significant difference in the time to endoscopic relapse within six months of treatment discontinuation between patients treated for up to 16 weeks compared to those treated for up to eight weeks (99.17 vs 97.46 days; *P*=0.3415). The proportions of patients with reflux esophagitis according to endoscopy and concomitant reflux symptoms were each significantly lower following pantoprazole treatment compared to baseline (*P*<0.0001). Overall, 175 patients (27.6%) experienced 277 treatment-emergent adverse events. Of these, 48 (17.3%) were considered by the investigator to be 'likely related' and four were assessed as 'definitely related' to treatment with pantoprazole. Seven treatment-emergent serious adverse events were reported (optic neuritis, colon cancer, stress urinary incontinence, myocardial ischemia, myocardial infarction, hand fracture and cerebrovascular accident) occurred in six patients (0.9%) during the study. All serious adverse events were considered by the investigator to be unrelated to pantoprazole treatment. Secondary: Not reported
Fujimoto et al[64] Rabeprazole 10 mg QD	ES, MC, OL, PRO Patients ≥20 years of age with reflux esophagitis who required a PPI for maintenance therapy (patients who relapsed, as proven	N=194 104 weeks	Primary: Proportion of patients remaining symptom-free, changes in gastric mucosal atrophy, gastric mucosal histology, serum gastrin and safety	Primary: Treatment with rabeprazole was associated with significant increases the proportion of relapse-free patients compared to baseline at week 24 (94.0%; (95% CI, 90.5 to 97.4), week 52 (91.0%; 95% CI, 86.7 to 95.2), week 76 (89.6%; 95% CI, 85.1 to 94.2) and week 104 (87.3%; 95% CI, 82.1 to 92.4). Grading of gastric mucosal atrophy was higher (worsened) in the *H pylori*-positive patients compared to the negative population.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	endoscopically or symptomatically after discontinuation of PPI treatment) and no esophageal mucosal injury (Los Angeles grades A, B, C or D)		Secondary: Not reported	By the end of the, study gastric mucosal atrophy had progressed in eight patients compared to baseline (5.8%; 95% CI, 2.5 to 11.0). There was no change in gastric mucosal atrophy in 123 subjects (88.5%). Histological changes demonstrated a statistically significant increase in grimelius stain at week 104 compared to baseline (*P*<0.01). There were no significant fluctuations in CgA immunostained positive cells throughout the treatment period. The mean change in serum gastrin level at 24 weeks was 44.0 pg/mL (95% CI, 16.4 to 71.6; *P*=0.01). The increase in serum gastrin remained significantly increased from baseline at week 52 (*P*<0.001), week 76 (*P*<0.01) and week 104 (*P*<0.001). The most frequently reported adverse drug reaction was increased blood pressure (three patients), followed by elevated blood triglycerides and toxic skin eruption (two events in two patients). Six patients withdrew from the study due to adverse events, which included toxic skin eruption (two cases), urticaria (one case), elevated blood pressure (one case), elevated blood triglycerides (one case), decreased white blood cell count and platelet count (one case each). Secondary: Not reported
Kinoshita et al[65] rabeprazole 5 mg QD vs rabeprazole 10 mg QD vs placebo	DB, MC, PC, RCT Patients ≥20 years of age with ≥2 days/week of heartburn episodes for three consecutive weeks prior to screening, endoscopy performed within 14 days of the observation period without any	N=not reported 4 weeks	Primary: Complete heartburn relief at the final evaluation (no episodes of heartburn for seven days immediately before evaluation)	Primary: Following four weeks of treatment, a significantly greater proportion of patients treated with rabeprazole 10 mg experienced complete heartburn relief compared to placebo (43.6 vs 20.9%; *P*=0.001). There was no significant difference between the rabeprazole 5 and 10 mg treatment group with regard to complete heartburn relief at four weeks (34.3 vs 43.6%; *P* value not reported). Secondary: A higher proportion of patients treated with rabeprazole 10 or 5 mg achieved complete heartburn relief at two weeks compared to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	medication influencing reflux symptom (PPI and antidepressant or anxiolytic agent)		Secondary: Complete heartburn relief rate at two and four weeks, satisfactory heartburn relief rate at two and four weeks after initiation of treatment and the final evaluation, percentage of heartburn-free days, time to first 24-hour heartburn-free interval (no heartburn for two consecutive periods)	(28 and 20 vs 10%); however, the difference was only significant with the 10 mg rabeprazole dose (*P*=0.003). More patients treated with either rabeprazole 10 or 5 mg daily achieved complete heartburn relief at four weeks compared to placebo (44 and 35 vs 21%); however, the difference was only statistically significant with the 10 mg dose. Satisfactory heartburn relief at two weeks was reported in 44 and 33% of patients treated with rabeprazole 10and 5 mg, respectively, compared to placebo (24%). The difference was only significant for patients receiving rabeprazole 10 mg daily (*P*=0.006). At week four, satisfactory heartburn relief was reported in a significantly greater proportion of patients treated with rabeprazole 10 mg compared to placebo (56 vs 35%; *P*=0.006). Satisfactory heartburn relief was also reported in a numerically higher proportion of patients receiving rabeprazole 5 mg (50%) compared to placebo, although the difference was not statistically significant (*P*=0.076). Both rabeprazole treatments significantly reduced the time to first 24-hour heartburn-free period compared to placebo (1 vs 3 days, respectively; *P*<0.05).
Laine et al[66] Rabeprazole extended-release 50 mg* QD vs esomeprazole 40 mg QD	2 AC, DB, MC, RCT Patients 18 to 75 years of age with a history of GERD symptoms for ≥3 months before screening, heartburn at least two days/week for ≥1 month before screening endoscopy and moderate-to-severe erosive GERD (Los Angeles grade C	N=2,130 8 weeks	Primary: Proportion of patients with endoscopically confirmed healing by week four and week eight Secondary: Proportion of patients who achieved a sustained	Primary: In study I, 80% of patients treated with rabeprazole experienced endoscopically confirmed healing by week eight compared to 75% in the esomeprazole group (95% CI, 0.0 to 10.0). In study II, there was no difference healing rates between patients treated with rabeprazole (77.5%) or esomeprazole (78.4%) by week eight of treatment (difference, 0.9; 95% CI, -5.9% to 4.0%). At week four, 54.8% of patients randomized to rabeprazole achieved healing compared to 50.3% of patients receiving esomeprazole in study I (*P*=0.162). In study II, the four-week healing rates were not significantly different

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	or D) at screening endoscopy; patients were excluded if they tested positive for *H pylori* in the month before screening endoscopy; current or history of esophageal motility disorders, Barrett's esophagus, esophageal strictures or esophagitis due to an etiology other than GERD, Zollinger-Ellison syndrome or other acid hypersecretory conditions or current gastric or duodenal ulcer		resolution of heartburn (seven or more consecutive days) at week four, and safety; exploratory endpoints included the time to first heartburn-free day, time to first resolution of heartburn, percentage of heartburn-free days and nights, investigator-recorded sustained resolution and other GERD symptoms at week four and week eight	between patients treated with rabeprazole or esomeprazole (50.9 vs 50.7%, respectively; *P*=0.828). Secondary: In study I, the proportion of patients with sustained heartburn resolution at four weeks was not significantly different between patients randomized to receive rabeprazole compared to esomeprazole (48.3 vs 48.2%, respectively; *P*=0.991). Similarly, no statistically significant difference in sustained resolution was apparent between the treatment groups at week four in study II (53.2 vs 52.5%; *P*=0.757). Treatment-emergent adverse events occurred in 289 (28%) patients treated with rabeprazole and 282 (27%) patients in the esomeprazole group. One percent of patients in each group discontinued treatment due to an adverse event. Diarrhea was the most frequently reported adverse event in both treatment groups. Two deaths were reported in the rabeprazole group (one each for acute coronary syndrome and head injury). In the ITT population, results for all the exploratory endpoints were comparable between the rabeprazole and esomeprazole treatment groups with no statistically significant differences reported.
Peptic Ulcer Disease				
Choi et al[67] Esomeprazole 40 mg BID vs omeprazole 20 mg BID vs pantoprazole 40 mg	PRO, RCT Patients who underwent upper endoscopy for various gastrointestinal symptoms with *H pylori* infection documented by histologic examinations	N=576 1 week	Primary: *H pylori* eradication rates and side effects Secondary: Not reported	Primary: In the ITT analysis, no difference was reported in the eradication rates between esomeprazole (70.3%), omeprazole (64.9%), pantoprazole (69.3%) and rabeprazole (69.3%; *P*=0.517). When eradication rates were analyzed by the presence of an ulcer, no significant difference was found between the eradication rates for the four PPIs (*P*=0.610). Eradication rates for patients with PUD were 84.2% for esomeprazole, 80.0% for omeprazole, 78.9% for pantoprazole and 82.8% for rabeprazole (*P*=0.833). Eradication rates for patients with nonnuclear dyspepsia were 87.5% for esomeprazole, 81.4% for omeprazole, 84.6% for pantoprazole and 73.1% for rabeprazole (*P*=0.412).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID vs rabeprazole 20 mg BID PPI therapy was administered for one week along with amoxicillin 1 g BID and clarithromycin 500 mg BID.				Adverse events were more common in the esomeprazole-based triple therapy group than in the other groups (*P*=0.038); however, the frequencies of individual symptoms were not significantly different among the four groups. Secondary: Not reported
Vergara et al[68] *H pylori* triple therapy with esomeprazole, lansoprazole, omeprazole, pantoprazole or rabeprazole	MA RCTs investigating *H pylori* triple therapy with a PPI with comparable antibiotic regimens differing only in the PPI utilized	14 trials 7 to 14 days	Primary: Direct comparison of eradication rates in the ITT population between PPIs Secondary: Not reported	Primary: Pooled eradication rates with omeprazole (74.7%) were comparable to rates observed with lansoprazole (76%; OR, 0.91; 95% CI, 0.69 to 1.21). Pooled eradication rates with omeprazole (77.9%) were comparable to rates observed with rabeprazole (81.2%; OR, 0.81; 95% CI, 0.58 to 1.15). Pooled eradication rates with omeprazole (87.7%) were comparable to rates observed with esomeprazole (89%; OR, 0.89; 95% CI, 0.58 to 1.35). Pooled eradication rates with lansoprazole (81.0%) were comparable to rates observed with rabeprazole (85.7%; OR, 0.77; 95% CI, 0.48 to 1.22). Secondary: Not reported
Ulmer et al[69] *H pylori* triple therapy with lansoprazole, omeprazole, or pantoprazole with two other antibiotics for seven days	MA Clinical trials using PPI-based triple therapy for seven days in *H pylori* infections	79 trials 7 days	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: Eradication rates for all therapies were 71.9 to 83.9% in the ITT population and 78.5 to 91.2% for the per-protocol analysis. Pooled data analysis indicated that lansoprazole-, omeprazole- or pantoprazole-based therapies are comparable in *H pylori* eradication. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gisbert et al[70] Esomeprazole-based *H pylori* therapies vs omeprazole-based *H pylori* therapies	MA RCTs investigating the use of esomeprazole-based *H pylori* therapies and other PPI-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	Number of trials analyzed not reported Treatment duration not reported	Primary: *H pylori* eradication rates for esomeprazole therapies Secondary: Comparison of eradication rates for esomeprazole compared to omeprazole therapy	Primary: Dual therapy with esomeprazole and clarithromycin therapy resulted in eradication rates of 51 to 54%. Mean eradication rates following triple therapy with esomeprazole, clarithromycin, and either amoxicillin or metronidazole were 82 to 86%. Secondary: Mean eradication rates for esomeprazole-based therapies (85%) were comparable to omeprazole-based therapies (82%; OR, 1.19; 95% CI, 0.81 to 1.74).
Wang et al[71] Esomeprazole-based *H pylori* therapies vs omeprazole- and pantoprazole-based *H pylori* therapies	MA RCTs investigating the use of esomeprazole-based *H pylori* therapies and other PPI-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	11 trials 1 week (*H pylori* eradication)	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: The mean *H pylori* eradication rates with esomeprazole-based therapies were comparable to that for other PPI-based regimens (86 vs 81%; OR, 1.38; 95% CI, 1.09 to 1.75). Subanalysis that included only studies comparing different doses of esomeprazole with omeprazole or pantoprazole did not reveal any statistically significant differences between the treatments. No serious adverse events were reported. Secondary: Not reported
Hsu et al[72] Esomeprazole 40 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for one week vs pantoprazole 40 mg	PRO, RCT Patients ≥18 years old, infected with *H pylori*, with endoscopically proven PUD or gastritis	N=200 8 weeks (follow-up endoscopy)	Primary: *H pylori* eradication rates, adverse events and compliance Secondary: Ulcer healing	Primary: The ITT analysis demonstrated a significantly higher eradication rate for patients in the esomeprazole group compared to for the pantoprazole group (94 vs 82%; *P*=0.009). Both groups had a similar frequency of adverse events (15 vs 24%) and drug compliance (97 vs 96%). Secondary: Patients who had peptic ulcers diagnosed by initial endoscopy showed similar

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for one week				ulcer healing rates with esomeprazole (36/40) and pantoprazole (38/42) therapy.
Wu et al[73] Esomeprazole 40 mg QD, amoxicillin 1 g BID and clarithromycin 500 mg BID for one week vs rabeprazole 20 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for one week	PRO, RCT Patients with gastritis or peptic ulcer with *H pylori* infection	N=420 12 to 16 weeks (follow-up)	Primary: *H pylori* eradication rates, adverse events and compliance Secondary: Not reported	Primary: The ITT analysis revealed that there was no statistically significant difference with regard to eradication rate in the esomeprazole group compared to the rabeprazole group (84.9 vs 90.5%; *P*=0.72). Compliance was reported in 100 and 99.5% of patients in the esomeprazole and rabeprazole groups, respectively (*P*=0.32). Adverse events were reported in 3.8 and 6.2% of patients in the esomeprazole and rabeprazole groups, respectively (*P*=0.27). Secondary: Not reported
Bazzoli et al[74] Lansoprazole-based *H pylori* therapies vs omeprazole-based *H pylori* therapies	MA RCTs investigating the use of lansoprazole-based *H pylori* therapies and other PPI-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	N=1,354 16 trials	Primary: *H pylori* eradication rates for lansoprazole therapies Secondary: Comparison of eradication rates for lansoprazole vs omeprazole therapy	Primary: Eradication rates for lansoprazole monotherapy (six to eight week duration) were comparable to dual therapy with lansoprazole (six to eight week duration) and amoxicillin (two to four week duration; OR, 0.8; 95% CI, 0.3 to 1.9 for gastric ulcers; OR, 1.5; 95% CI, 0.4 to 5.7 for duodenal ulcers). The mean eradication rates for triple therapy with lansoprazole were significantly higher compared to dual lansoprazole therapy (91.8 vs 57.1%; OR, 8.5; 95% CI, 2.9 to 24.5). Secondary: Mean eradication rates for lansoprazole-based therapies (80.6%) were comparable to omeprazole-based therapies (69.6%; OR, 0.9; 95% CI, 0.6 to 1.3).
Gisbert et al[75] Pantoprazole-based *H pylori* therapies vs	MA RCTs investigating the use of pantoprazole-based *H pylori* therapies and	12 trials Treatment duration not reported	Primary: *H pylori* eradication rates for pantoprazole therapies	Primary: Fourteen-day therapy with pantoprazole 40 mg and clarithromycin 500 mg therapy resulted in a mean eradication rate of 60%. Mean eradication rates following seven-day therapies were as follows: pantoprazole-amoxicillin-clarithromycin 78%, pantoprazole-clarithromycin-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lansoprazole- or omeprazole-based *H pylori* therapies	lansoprazole- or omeprazole-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized		Secondary: Comparison of eradication rates for pantoprazole compared to other similar (same antibiotics and duration of use) PPI therapies, comparison of pantoprazole therapies to similar omeprazole and lansoprazole therapies	nitroimidazole 84% and pantoprazole-amoxicillin-nitroimidazole 74%. Secondary: Mean eradication rates for pantoprazole-based therapies with antibiotics were comparable to other PPI-based therapies (83 vs 81%; OR, 1.00; 95% CI, 0.61 to 1.64). Mean eradication rates for pantoprazole-based therapies were comparable to omeprazole-based therapies (83 vs 82%; OR, 0.91; 95% CI, 0.49 to 1.69). Mean eradication rates for pantoprazole-based therapies (78%) were comparable to those with lansoprazole-based therapies (75%; OR, 1.22; 95% CI, 0.68 to 2.17).
Felga et al[76] Omeprazole or other PPI (dose not specified) BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for one week	OL Patients with current or previous PUD and documented *H pylori* infection through a positive urea breath test, serology, rapid urease test, or histological examination of gastric mucosa; patients were excluded if they were <18 years of age, presented with a severe comorbidity, pregnancy, infants, patients who had previously undergone gastrectomy, allergy	N=493 7 days	Primary: Eradication rates 12 weeks following completion of therapy and adverse events Secondary: Not reported	Primary: In the ITT population, the eradication rate was 88.8% (95% CI, 86 to 92) at 12 weeks and 82.7% (95% CI, 79 to 86) in the per-protocol population. Adverse events were reported in 35.5% of treated patients; however only six (7%) of these patients discontinued treatment due to adverse events. Tobacco use and NSAID use were associated with an increase in frequency of adverse events. The most commonly reported adverse events were abdominal pain, nausea, vomiting, diarrhea and taste perversion. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	to study medications, and patients who used NSAIDs, antibiotic therapy, or bismuth salts up to four weeks before study inclusion.			
McNicholl et al[77] Rabeprazole- or esomeprazole based *H pylori* therapies vs lansoprazole-, omeprazole- or pantoprazole based *H pylori* therapies	MA RCTs investigating the use of rabeprazole- or esomeprazole-based *H pylori* therapies compared to first-generation PPIs (omeprazole-lansoprazole-pantoprazole) or with one another	N=35 trials Treatment duration not reported	Primary: *H pylori* eradication rates based Secondary: Not reported	Primary: Compared to first-generation PPIs, rabeprazole demonstrated a higher eradication rate in patients with *H pylori* (80.5 vs 76.2%). The OR was 1.21 (95% CI, 1.02 to 1.42) and the NNT was 23. Esomeprazole treatment was associated with a higher *H pyl*ori eradication compared to the first generation PPIs (82.3 vs 77.6%, respectively). The OR for eradication was 1.32 (95% CI, 1.01 to 1.73) and the NNT was 21. Subanalyses by dose indicated that only treatment with esomeprazole 40 mg BID significantly improved eradication rates compared to esomeprazole therapy with either dose (OR, 2.27; 95% CI, 1.07 to 4.82; NNT, 9). There was no statistically significant difference in *H pylori* eradication rates between rabeprazole-and esomeprazole-based treatment regimens (OR, 0.90, 95% CI, 0.70 to 1.17). The NNT was 50. There was no statistically significant difference in eradication rates with rabeprazole- or esomeprazole-based therapies in CYP2C19 poor metabolizers compared to extensive metabolizers (OR, 1.19; 95% CI, 0.73 to 1.95). Similarly, no differences in eradication rates occurred between CYP2C19 poor metabolizers and extensive metabolizers (OR, 1.76; 95% CI, 0.99 to 3.12). There was no statistically significant difference in eradication rates between rabeprazole- and esomeprazole based therapies compared to first generation

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				PPIs with on the basis of poor CYP2C19 metabolism (OR, 0.91; 95% CI, 0.41 to 1.98). There was a statistically significant increase in *H pylori* eradication rate with rabeprazole- and esomeprazole-based regimens compared to first generation PPIs in patients who were extensive CYP2C19 metabolizers (OR, 1.37, 95% CI, 1.02 to 1.84).
Gisbert et al[78] Rabeprazole-based *H pylori* therapies vs lansoprazole- or omeprazole-based *H pylori* therapies	SR RCTs investigating the use of rabeprazole-based *H pylori* therapies and lansoprazole- or omeprazole-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	12 trials Treatment duration not reported	Primary: *H pylori* eradication rates for rabeprazole therapies Secondary: Comparison of eradication rates for rabeprazole compared to other similar (same antibiotics and duration of use) PPI therapies, comparison of rabeprazole therapies to similar omeprazole and lansoprazole therapies	Primary: Rabeprazole dual therapy with amoxicillin for 14 days resulted in a mean eradication rate of 73%. Mean eradication rates for low-dose rabeprazole (20 mg/day) triple therapy with amoxicillin and clarithromycin for seven days were 81 and 75% with high-dose rabeprazole (40 mg/day). Mean eradication rate for rabeprazole triple therapy with a nitroimidazole and clarithromycin for seven days was 85%. Secondary: Mean eradication rate for rabeprazole-based therapies (79%) with antibiotics was comparable to other PPI-based therapies (77%; OR, 1.15; 95% CI, 0.93 to 1.42). Mean eradication rates for rabeprazole-based therapies (77%) were comparable to omeprazole-based therapies (77%; OR, 1.03; 95% CI, 0.81 to 1.32). Mean eradication rates for rabeprazole-based therapies (82%) were comparable to lansoprazole-based therapies (79%; OR, 1.17; 95% CI, 0.79 to 1.74).
Other				
Scheiman et al[79] OBERON Esomeprazole 20 mg QD	DB, MC, PC, PG, RCT Patients ≥18 years of age taking low-dose ASA (75 to 325	N=2,426 26 weeks	Primary: Endoscopy-confirmed peptic (gastric or duodenal) ulcer	Primary: In the ITT population, the incidence of peptic ulcer during treatment was 1.5% (95% CI, 0.6 to 2.4) in patients receiving esomeprazole 40 mg, 1.1% (95% CI, 0.3 to 1.9) in the esomeprazole 20 mg group and 7.4% (95% CI, 5.5 to 9.3) in the placebo group (*P*<0.0001 for both esomeprazole doses compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs esomeprazole 40 mg QD vs placebo	mg/day) who were *H pylori* negative with one or more of the following: a documented history of uncomplicated peptic ulcer; aged ≥60 years with one or more risk factor (stable coronary artery disease, or complaints of upper gastrointestinal symptoms that, as judged by the investigator, required an endoscopy resulting in a finding of five or more gastric and/or duodenal erosions at baseline endoscopy, or low-dose ASA-naïve or aged ≥65 years; patients at very high cardiovascular and/or gastrointestinal risk were excluded		during treatment Secondary: Occurrence of a gastric ulcer and, separately, a duodenal ulcer, during treatment, safety and tolerability	to placebo). The RRR with esomeprazole 40 mg compared to placebo was 80, and 85% in esomeprazole 20 mg recipients. The absolute risk reductions were of 5.9 and 6.3%, respectively. Secondary: In the ITT population, gastric ulcers were more prevalent than duodenal ulcers in all treatment groups. Patients treated with esomeprazole 40 mg experienced a 74 and 90% RRR in gastric and duodenal ulcers, respectively, compared to placebo (*P*<0.001 for both) Similarly, patients randomized to receive esomeprazole 20 mg experienced RRRs of 83 and 90%, respectively (*P*<0.0001 for both). Statistically significant reductions in peptic ulcers were reported with esomeprazole regardless of aspirin dose (*P*≤0.02 for both esomeprazole doses compared to placebo). Upper gastrointestinal complications occurred in two patients treated with esomeprazole 20 mg (hematemesis and distal duodenal perforation), three placebo recipients receiving placebo (two patients reported melena and one reported and experienced a decreased hemoglobin level) and no patients receiving esomeprazole 40 mg. Adverse events were reported with a similar frequency in the three treatment groups. The most commonly reported adverse events were diarrhea, headache and bronchitis. Nine deaths occurred during the study (four esomeprazole 40 mg, four esomeprazole 20 mg and one placebo recipient); however, none was considered to be related to esomeprazole. Serious adverse events other than death occurred in 5.3% of esomeprazole 40 mg, 4.9% of esomeprazole 20 mg and 4.4% of placebo recipients, none of which were considered study-drug related.
Ramdani et al[80] Lansoprazole 30 to 120 mg/day or omeprazole	OL, PRO Adult patients with Zollinger-Ellison	N=11 7 to 10 days	Primary: Median 24-hour intragastric pH and percentage of	Primary: Median 24-hour intragastric pH for pantoprazole (5.3) was comparable to the median pH for lansoprazole and omeprazole (4.6 for both agents; *P*=0.90).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
20 to 100 mg/day vs pantoprazole 40 to 200 mg/day If previously maintained on lansoprazole or omeprazole received pantoprazole for 7 to 10 days.	syndrome maintained on omeprazole or lansoprazole; patients were excluded if they had a history of gastric or esophageal surgery, gastrointestinal malignancy, or a significant unstable disease		time at or below pH 3, 4, 5 and 6 Secondary: Basal acid output	There were no significant differences in percentage of time at or below pH 3, 4, 5 and 6 between pantoprazole and lansoprazole or omeprazole (*P*>0.05). Secondary: Median basal acid output was similar between pantoprazole and lansoprazole or omeprazole (*P* value not reported).
Sugano et al[81] Lansoprazole 15 mg QD vs gefarnate* 50 mg BID	AC, DB, MC, PC, RCT Patients receiving low-dose aspirin a history of gastric or duodenal ulcer (or gastroduodenal ulcer) was confirmed by endoscopy, (i.e., confirmed ulcer scar on day one or were confirmed to have an ulcer or ulcer scar in an endoscopic exam performed prior to day one (e.g., photographs, films).	N=461 12 months	Primary: Recurrence of gastric or duodenal ulcers, (confirmed active-stage or healing-stage ulcers with a mucosal defect measuring ≥3 mm) Secondary: Development of gastric and/or duodenal hemorrhagic lesions observed on endoscopy, treatment discontinuations due to lack of efficacy, gastric and/or duodenal mucosal damage	Primary: After 12 months of treatment, the cumulative number of confirmed gastric or duodenal ulcers was significantly lower in patients treated with lansoprazole compared to gefarnate (6 vs 53; *P*<0.001). After 91 days of treatment, the recurrence rate was 1.5% (95% CI, 0.00 to 3.20) in the lansoprazole group compared to 15.2% (95% CI 10.17 to 20.22) in the gefarnate group. After 181 days of treatment, gastric/duodenal ulcer recurrence rates were 2.1% (95% CI, 0.06 to 4.08) in the lansoprazole group and 24.0% (95% CI, 17.84 to 30.21) in patients receiving gefarnate. Lansoprazole therapy was associated with a lower incidence of ulcer recurrence at day 381 (3.7%; 95% CI, 0.69 to 6.65) compared to patients randomized to gefarnate (31.7%; 95% CI, 23.86 to 39.57). Secondary: Patients treated with lansoprazole experienced significantly fewer gastric/duodenal ulcers or hemorrhagic lesions compared to patients treated with gefarnate over 12 months (7 vs 56; *P*<0.0010. The risk of having gastric/duodenal ulcers, hemorrhagic lesions, or treatment discontinuations due to lack of efficacy was significantly lower in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			(assessed with a modified Lanza score) and gastrointestinal symptoms	lansoprazole group than in the gefarnate group (7 vs 59; *P*<0.001). Gastrointestinal damage, assessed by a modified Lanza score, improve in the lansoprazole group, but worsened in the gefarnate group, throughout the course of treatment. Compared to gefarnate, treatment with lansoprazole was associated with a lower incidence of gastric ulcer (6 vs 40), duodenal ulcer (0 vs 15) hemorrhagic lesion (2 vs 9) and treatment discontinuations due to lack of efficacy (0 vs 4; *P* values not reported). Diarrhea was occurred significantly more frequently in lansoprazole-treated patients compared to the gefarnate group. Reflux esophagitis was significantly more frequent with gefarnate compared to lansoprazole. There were no serious adverse events in the lansoprazole treatments group while one serious event (liver disorder) occurred with gefarnate. There were no deaths in either group.
Conrad et al[82] Omeprazole suspension (two 40 mg dose on day one then 40 mg/day thereafter) vs cimetidine intravenous (300 mg bolus then 50 mg/hour thereafter)	DB, RCT Hospitalized patients >16 years old in the intensive care unit with an anticipated stay ≥72 hours with >1 additional risk for upper gastrointestinal bleed; patients were excluded for history of gastric surgery, allergy to cimetidine or omeprazole, active gastrointestinal bleeding, significant risk of swallowing blood, enteral feeding required for the first two	N=359 14 days	Primary: Clinically significant upper gastrointestinal bleed Secondary: Median gastric pH on each trial day, percentage of patients with median gastric pH >4 on each trial day and the percentage of patients with inadequate gastric pH control (two consecutive pH	Primary: Clinically significant upper gastrointestinal bleeding was observed in seven (3.9%) patients taking omeprazole compared to ten (5.5%) patients taking cimetidine (*P* value not reported). The upper bound of the one-sided 97.5% CI for the difference in bleeding rates was 2.8%, less than the 5% prespecified NI margin. Secondary: Median gastric pH was significantly higher in patients taking omeprazole compared to cimetidine (median pH values not reported; *P*<0.001). A significantly higher percentage of patients on omeprazole had median daily gastric pH >4 compared to patients on cimetidine (*P*≤0.01 on days one to 13, *P*=0.2 on day 14). A significantly higher percentage of patients on cimetidine had inadequate gastric pH control (58%) compared to omeprazole (18%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	days of the trial, admission for upper gastrointestinal surgery, known upper gastrointestinal lesions that might bleed, the inability to take a suspension by nasogastric tube or end-stage liver disease		measurements of ≤4)	
Katz et al[83] Omeprazole suspension 40 mg for seven days vs esomeprazole 40 mg for seven days vs lansoprazole 30 mg for seven days Following a 10 to 14 day washout between treatment periods, patients were XO to one of the alternative treatments.	OL, RCT, XO Non-Asian patients ≥18 years of age with a history of GERD at least partially responsive to antacids or acid suppressants and had recurrent night-time symptoms for the previous three months, baseline gastric pH ≤2.5 prior to randomization; patients were excluded for concurrent gastrointestinal diseases other than GERD, a significant history of gastrointestinal diseases in the past five years and any history of gastric surgery or any other significant unstable	N=54 21 days (XO at 7 days)	Primary: Occurrence of nocturnal acid breakthrough (gastric pH <4 for more than one hour during the night-time from 22:00 to 06:00 hours) Secondary: Percentage of time gastric pH>4 and median gastric pH in cumulative two-hour increments during the nighttime period and over 24 hours	Primary: After seven days of bedtime dosing, omeprazole significantly reduced nocturnal acid breakthrough compared to esomeprazole and lansoprazole (61 vs 92 and 92%; *P*<0.001 for both comparisons). Secondary: During the first half of the night, percentage of time with gastric pH >4 and median gastric pH were significantly higher after omeprazole (52% and 4.34, respectively) compared to esomeprazole (30% and 2.37, respectively) or lansoprazole (12% and 1.51, respectively; *P*<0.001 for both comparisons). Over the eight hour nighttime period, the percentage of time with gastric pH >4 and median gastric pH were significantly higher after omeprazole (53% and 4.04, respectively) than lansoprazole (34% and 2.09, respectively; *P*<0.001 for both comparisons) but comparable to esomeprazole (55% and 4.85, respectively). The percentage of time with gastric pH >4 for the 24-hour period was 44% with omeprazole compared to 59% with esomeprazole (*P*<0.001) and 28% with lansoprazole (*P*<0.001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	illness			
Castell et al[84] Omeprazole suspension dosed 40 mg/day for one week, then 20 or 40 mg BID for one day vs pantoprazole 40 mg/day for one week, then 40 mg BID for one day Participants underwent eight days of treatment followed by a 10 to 14 day washout period then an additional eight days of treatment on the other agent.	OL, RCT, XO Adult patients 18 to 65 years old with GERD and recurrent nighttime symptoms for the previous three months; patients were excluded if they had current gastrointestinal disease other than GERD, history of gastric surgery, other significant, unstable disease or use of any gastric antisecretory drugs seven days prior to the trial	N=36 16 days	Primary: Control of nocturnal gastric acidity measured by the following: percentage of time with gastric pH >4, median gastric pH and nocturnal acid breakthrough Secondary: Not reported	Primary: Median percentage of time with gastric pH >4 was significantly higher with omeprazole (54.7%) compared to pantoprazole (26.5%; *P*<0.001). Median gastric pH was significantly higher with omeprazole (4.7) compared to pantoprazole (2.0; *P*<0.001). Significantly less nocturnal acid breakthrough was observed with omeprazole (53.1%) compared to pantoprazole (78.1%; *P*=0.005). Secondary: Not reported
Regula et al[85] Omeprazole 20 mg QD vs pantoprazole 20 mg QD vs pantoprazole 40 mg QD	DB, MC, PG, RCT Rheumatic patients >55 years of age on continual NSAIDs and with ≥1 recognized risk factor that contributes to the development of gastrointestinal injury; patients were excluded if they had Zollinger-Ellison syndrome, esophageal structures,	N=595 6 months	Primary: Therapeutic failure (peptic ulcer, >10 erosions or petechiae in the stomach or duodenum, reflux esophagitis, or discontinuation due to gastrointestinal symptoms or an adverse event)	Primary: After six months, the probabilities of remaining in remission were 90% with pantoprazole 20 mg, 93% with pantoprazole 40 mg and 89% with omeprazole for lack of therapeutic failure (*P* values not reported). After six months, the probabilities of remaining in remission remission were 91% with pantoprazole 20 mg, 95% with pantoprazole 40 mg and 93% with omeprazole for lack of endoscopic failure (*P* values not reported). During the study, a similar proportion of patients reported adverse events in each treatment group (29% of patients receiving pantoprazole 20 mg; 37% of patients receiving pantoprazole 40 mg and 33% of patients receiving omeprazole; *P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	previous surgery of the gastrointestinal tract, current peptic ulcer or peptic ulcer complication		and lack of endoscopic failure at six months and adverse events Secondary: Primary end points at three months	Secondary: After three months, the probabilities of remaining in remission remission were 94% with pantoprazole 20 mg, 97% with pantoprazole 40 mg and 94% with omeprazole for lack of therapeutic failure (*P* values not reported). After three months, the probabilities of remaining in remission were 96% with pantoprazole 20 mg, 99% with pantoprazole 40 mg and 96% with omeprazole for lack of endoscopic failure (*P* values not reported).
Chan et al[86] Diclofenac (slow release) 75 mg BID plus omeprazole 20 mg QD vs celecoxib 300 mg BID	DB, PG, RCT, TD Patients ≥60 years of age with a clinical diagnosis of osteoarthritis or rheumatoid arthritis who were expected to need regular NSAID treatment for ≥6 months, with or without a history of gastroduodenal ulceration or gastrointestinal hemorrhage and *H pylori negative* (patients 18 to 59 years of age were enrolled if they had a documented history of gastroduodenal ulceration or gastrointestinal hemorrhage ≥90 days before screening)	N=4,484 6 months	Primary: Composite of clinically significant events occurring throughout the gastrointestinal tract Secondary: Patients' Global Assessment of Arthritis, clinically significant events throughout the gastrointestinal tract plus symptomatic ulcer, moderate-to-severe abdominal symptoms and withdrawal due to gastrointestinal adverse events	Primary: Twenty primary endpoints (gastroduodenal ulcer, small-bowel or large-bowel hemorrhage; gastric-outlet obstruction; gastroduodenal, small-bowel or large-bowel perforation; clinically significant anemia of defined gastrointestinal or presumed occult gastrointestinal origin [including possible blood loss from the small-bowel] and acute gastrointestinal hemorrhage of unknown origin [including presumed small-bowel hemorrhage]) in patients receiving celecoxib and 81 in patients taking diclofenac plus omeprazole were identified. The proportion of patients reaching the primary endpoint during the six month period was 0.9% (95% CI, 0.5 to 1.3) in the celecoxib group and 3.8% (95% CI, 2.9 to 4.3) in the diclofenac plus omeprazole (difference, 2.9%; 95% CI, 2.0 to 3.8; *P*<0.0001, with a corresponding HR of 4.3 (95% CI, 2.6 to 7.0) in favor of celecoxib. The main driving force behind the primary endpoint was a hemoglobin decrease of ≥20 g/L. Fewer celecoxib-treated patients had a significant decrease in hemoglobin (15 vs 77; *P* value not reported). Secondary: The least-squares mean change from baseline to visit six in Patients' Global Assessment of Arthritis demonstrated an improvement of 0.75 (0.02) in the celecoxib group and 0.77 (0.02) in the diclofenac plus omeprazole group (*P*=0.41). Regarding clinically significant events throughout the gastrointestinal tract plus symptomatic ulcers (defined as ulcer on endoscopy in a patient with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				dyspepsia), fewer events were reported for patients who received celecoxib (N=25; 1%) than for patients who received diclofenac plus omeprazole (N=92; 5%; *P*<0.0001). The number of patients with moderate-to-severe abdominal symptoms at month six was 336 (16%) for the celecoxib group and 384 (19%) for the diclofenac plus omeprazole group (*P*=0.03). One hundred and fourteen (6%) patients in the celecoxib group and 167 (8%) in the diclofenac plus omeprazole group withdrew early because of gastrointestinal adverse events (*P*=0.0006).

Drug regimen abbreviations: BID=twice daily, IR=immediate-release, QD=once daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open-label, OR=odds ratio, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, RRR=relative risk reduction, SB=single-blind, SR=systematic review, TD=triple-dummy, XO=crossover
Miscellaneous abbreviations: ASA=acetylsalicylic acid, CgA=chromogranin A, CYP21C9=cytochrome P450 2C19, GERD=gastroesophageal reflux disease, GSRS= gastrointestinal symptoms rating scale, H2RA=histamine-2 receptor antagonist, *H pylori=Helicobacter pylori*, ITT=intent to treat, N-GSSIQ=nocturnal gastroesophageal reflux disease symptom severity and impact questionnaire, NNT=number needed to treat, NSAIDs=nonsteroidal anti-inflammatory drugs, PAGI-QOL=patient assessment of upper gastrointestinal quality of life questionnaire, PAGI-SYM=patient assessment of upper gastrointestinal symptom severity index, PPI=proton-pump inhibitor, PGWB=psychological general well-being, PSQI=Pittsburgh sleep quality index, PUD=peptic ulcer disease, VAS=visual analog scale, WPAI=work productivity and activity impairment

Special Populations

Table 5. Special Populations[4-15,28]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Dexlansoprazole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Hepatic dose adjustment is recommended; a maximum dose of 30 mg should be considered in patients with moderate hepatic impairment.	B	Unknown
Esomeprazole magnesium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children >1 month of age.	No dosage adjustment required.	No dosage adjustment required for mild-to-moderate liver impairment. Hepatic dose adjustment is required in patients with severe liver impairment; do not exceed a dose of 20 mg.	B	Unknown
Esomeprazole sodium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children >1 month of age.	No dosage adjustment required.	No dosage adjustment required for mild-to-moderate liver impairment. Hepatic dose adjustment is required in patients with severe liver impairment; do not exceed a dose of 20 mg.	B	Unknown
Lansoprazole	No evidence of overall differences in safety or efficacy observed between elderly	No dosage adjustment required.	Hepatic dose adjustment should be considered in severe liver disease.	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	and younger adult patients. Approved for use in children >1 year of age.				
Omeprazole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children >1 year of age.	No dosage adjustment required.	Hepatic dose adjustment should be considered for the maintenance of healing of erosive esophagitis.	C	Yes (<7%)
Omeprazole magnesium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children >1 year of age.	No dosage adjustment required.	Hepatic dose adjustment should be considered for the maintenance of healing of erosive esophagitis.	C	Yes (<7%)
Omeprazole with sodium bicarbonate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Hepatic dose adjustment should be considered for the maintenance of healing of erosive esophagitis.	C	Yes (<7%)
Pantoprazole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	No dosage adjustment required.	No dosage adjustment required.*	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Approved in children ≥5 years of age.				
Rabeprazole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children ≥12 years of age.	No dosage adjustment required.	No dosage adjustment required for mild-to-moderate liver impairment. Caution is advised for patients with severe liver impairment.	B	Unknown

*Doses >40 mg/day have not been studied in patients with hepatic impairment.

Adverse Drug Events

Table 6 summarizes the most common adverse events associated with oral administration of the proton-pump inhibitors (PPIs). The PPIs are generally well tolerated with abdominal pain, diarrhea, flatulence, headache, nausea and vomiting reported as the most frequent side effects. Long-term use of PPIs for five or more years has been associated with an increase in hip fractures.[4-15,91] When administered for seven or more years, PPIs have been associated with a significantly increased risk of an osteoporosis-related fracture. At this time, there is inadequate evidence to mandate bone density studies and calcium supplementation in patients receiving chronic PPI therapy.[18] Additional studies are needed to determine the value of osteoprotective medications for patients receiving long-term therapy with PPIs.[91]

Table 6. Adverse Drug Events (%)[4-15,28]

Adverse Event(s)	Dexlansop-razole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansop-razole	Omep-razole	Omeprazole Magnesium	Omeprazole/ Sodium Bicarbonate	Pantop-razole	Rabep-razole
Cardiac Disorders									
Atrial fibrillation	-	-	-	-	-	-	6.2*	-	-
Bradycardia	-	-	-	-	-	-	3.9*	-	-
Supraventricular tachycardia	-	-	-	-	-	-	3.4*	-	-
Tachycardia	-	-	-	-	-	-	3.4*	-	-
Ventricular tachycardia	-	-	-	-	-	-	4.5*	-	-
Central Nervous System									
Anxiety	-	-	-	-	-	-	-	≥1	-
Asthenia	-	-	-	-	1.1 to 1.3	1.1 to 1.3	1.1 to 1.3	≥1	-
Dizziness	-	-	2.5	-	1.5	1.5	1.5	≥1	-
Fatigue	-	-	-	a	-	-	-	-	-
Headache	-	1.9 to 8.1	10.9	a	2.9 to 6.9	2.9 to 6.9	2.9 to 6.9	2 to 9	5.4 to 9.9
Somnolence	-	1.9	-	-	-	-	-	-	-
Dermatological									
Erythema multiforme	-	a	-	-	-	-	-	-	-
Rash	-	-	-	-	1.5	1.5	1.5	≤2	-
Stevens-Johnson syndrome	-	a	-	-	-	-	-	a	a
Toxic epidermal necrolysis	-	a	-	-	-	-	-	a	-
Endocrine and Metabolic									
Liver function abnormalities	-	-	-	-	-	-	1.7*	2	-
Gastrointestinal									
Abdominal pain	3.5 to 4.0	2.7 to 3.8	5.8	1.8 to 2.1	2.4 to 5.2	2.4 to 5.2	2.4 to 5.2	1 to 4	3.6
Acid regurgitation	-	-	-	-	1.9	1.9	1.9	-	-
Atopic gastritis	-	-	-	-	-	-	-	a	-
Constipation	-	a	2.5	1	1.1 to 1.5	1.1 to 1.5	1.1 to 4.5	≥1	2
Diarrhea	4.7 to 5.1	1 to 10	3.9	<8	3.0 to 3.7	3.0 to 3.7	3.0 to 3.9	2 to 6	4.5
Dry mouth	-	a	3.9	-	-	-	-	-	-

Adverse Event(s)	Dexlansop-razole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansop-razole	Omep-razole	Omeprazole Magnesium	Omeprazole/ Sodium Bicarbonate	Pantop-razole	Rabep-razole
Dyspepsia	-	-	6.4	-	-	-	-	≥1	-
Flatulence	1.4 to 2.6	a	10.3	-	2.7	2.7	2.7	2 to 4	3
Gastric hypomotility	-	-	-	-	-	-	1.7	-	-
Gastroenteritis	-	-	-	-	-	-	-	≥1	-
Hepatotoxicity	-	-	-	-	a	a	a	-	-
Nausea	2.8 to 3.3	1 to 10	6.4	≤3.7	2.2 to 4.0	2.2 to 4.0	2.2 to 4.0	2	1.8 to 4.5
Pancreatitis	-	a	-	-	a	a	a	-	-
Vomiting	1.4 to 2.2	-	-	-	1.5 to 3.2	1.5 to 3.2	1.5 to 3.2	2	3.6
Genitourinary									
Interstitial nephritis	-	-	-	-	a	a	a	-	-
Urinary tract infection	-	-	-	-	-	-	2.2*	≥1	-
Hematologic									
Thrombocytopenia	-	-	-	-	-	-	10.1*	a	-
Infections and Infestations									
Candidal infection	-	-	-	-	-	-	1.7*	-	-
Oral candidiasis	-	-	-	-	-	-	3.9*	-	-
Sepsis	-	-	-	-	-	-	5.1*	-	-
Laboratory Test Abnormalities									
Elevated serum glutamic pyruvic transaminase	-	-	-	-	-	-	-	≥1	-
Metabolism and Nutrition Disorders									
Fluid overload	-	-	-	-	-	-	5.1*	-	-
Hyperglycemia	-	-	-	-	-	-	10.7*	-	-
Hyperkalemia	-	-	-	-	-	-	2.2*	-	-
Hypernatremia	-	-	-	-	-	-	1.7*	-	-
Hypocalcemia	-	-	-	-	-	-	6.2*	-	-
Hypoglycemia	-	-	-	-	-	-	3.4*	-	-
Hypokalemia	-	-	-	-	-	-	12.4*	-	-
Hypomagnesemia	-	-	-	-	-	-	10.1*	-	-
Hyponatremia	-	-	-	-	-	-	3.9*	-	-
Hypophosphatemia	-	-	-	-	-	-	6.2*	-	-
Musculoskeletal									
Arthralgia	-	-	-	-	-	-	-	≥1	-
Back pain	-	-	-	-	1.1	1.1	1.1	≥1	-
Hip fracture	-	a	-	a	a	a	a	a	a

Adverse Event(s)	Dexlansop-razole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansop-razole	Omep-razole	Omeprazole Magnesium	Omeprazole/ Sodium Bicarbonate	Pantop-razole	Rabep-razole
Pain	-	-	-	-	-	-	-	-	3
Rhabdomyolysis	-	a	-	a	a	a	a	a	a
Respiratory									
Acute respiratory distress syndrome	-	-	-	-	-	-	3.4*	-	-
Bronchitis	-	-	-	-	-	-	-	≥1	-
Cough	-	-	-	-	1.1	1.1	1.1	≥1	-
Dyspnea	-	-	-	-	-	-	-	≥1	-
Nosocomial pneumonia	-	-	-	-	-	-	11.2*	-	-
Pharyngitis	-	-	-	-	-	-	-	≥1	3
Pneumothorax	-	-	-	-	-	-	0.6*	-	-
Respiratory failure	-	-	-	-	-	-	1.7*	-	-
Rhinitis	-	-	-	-	-	-	-	≥1	-
Sinusitis	-	-	1.7	-	-	-	-	≥1	-
Upper respiratory tract infection	1.7 to 2.9	-	1.1	-	1.9	1.9	1.9	≥1	-
Other									
Adverse events related to test procedure	-	-	23.1	-	-	-	-	-	-
Agitation	-	-	-	-	-	-	3.4*	-	-
Anemia	-	-	-	-	-	-	2.2 to 7.9	-	-
Application site reaction	-	-	1.7	-	-	-	-	-	-
Decubitus ulcer	-	-	-	-	-	-	3.4*	-	-
Fever	-	-	-	-	a	a	a	-	-
Flu-like syndrome	-	-	-	-	-	-	-	≥1	-
Hyperpyrexia	-	-	-	-	-	-	4.5*	-	-
Hypertension	-	-	-	-	-	-	7.9*	-	-
Hypotension	-	-	-	-	-	-	9.6*	-	-
Infection	-	-	-	-	-	-	-	-	2
Oedema	-	-	-	-	-	-	1.7*	-	-
Pruritus	-	-	1.1	-	-	-	-	-	-
Pyrexia	-	-	-	-	-	-	20.2*	-	-
Rash	-	-	-	-	-	-	5.6*	-	-

a Percent not specified.
- Event not reported or incidence <1%.
* Critically ill patients who were administered omeprazole sodium bicarbonate.

Contraindications

Table 7. Contraindications[4-15,28]

Contraindication	Dexlansop-razole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansop-razole	Omep-razole	Omeprazole Magnesium	Omeprazole/ Sodium Bicarbonate	Pantop-razole	Rabep-Razole
Hypersensitivity to benzimidazoles	-	a	a	-	-	-	-	a	a
Known hypersensitivity to any component of the formulation	a	-	-	a	a	a	a	a	a

Warnings/Precautions

Table 8. Warnings and Precautions[4-15,28]

Warning/Precaution	Dexlansop-razole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansop-razole	Omep-razole	Omeprazole Magnesium	Omeprazole/ Sodium Bicarbonate	Pantop-razole	Rabep-Razole
Atrophic gastritis; occasionally reported with long-term therapy	-	a	a	-	a	a	a	a	-
Bone fracture; observational studies suggest a risk of osteoporotic fractures with high doses, or multiple daily doses for an extended period. Use lowest dose and shortest duration needed to control symptoms	a	a	a	a	a	a	a	a	a
Buffer content; sodium concentrations should be considered when administering to patients on a sodium restricted diet	-	-	-	-	-	-	a	-	-
Combination use with amoxicillin; pseudomembranous colitis has been reported with nearly all antibacterial agents and this diagnosis should be considered in patients presenting with diarrhea following the initiation of	-	a	a	-	a	a	-	-	a

Warning/Precaution	Dexlansop-razole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansop-razole	Omep-razole	Omeprazole Magnesium	Omeprazole/ Sodium Bicarbonate	Pantop-razole	Rabep-Razole
antibacterial treatment									
Combination use with amoxicillin; serious and occasionally fatal anaphylaxis has been reported in patients with penicillin allergies	-	a	a	-	a	a	-	-	a
Combination use with clarithromycin; use in pregnant women should be avoided except in circumstances where no alternative is available	-	a	a	-	a	a	-	-	a
Concurrent use with rifampin; substantially decreased serum concentrations of the substrate may occur and concomitant treatment should be avoided	-	a	a		a	a	-	-	-
Concurrent use with St. John's Wort; substantially decreased serum concentrations of the substrate may occur and concomitant treatment should be avoided	-	a	a	-	a	a	-	-	-
Concurrent use with warfarin; increased international normalized ratio and prothrombin time have been reported	-	-	-	-	-	-	-	-	a
Cyanocobalamin deficiency; daily antacid treatment for an extended period of time may lead to malabsorption due to hypo- or achlorhydria	-	-	-	-	-	-	-	a	-
Diminished antiplatelet activity of clopidogrel; avoid coadministration of omeprazole and clopidogrel due to an inhibitory effect of omeprazole on	-	-	-	-	a	a	-	-	-

Warning/Precaution	Dexlansop-razole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansop-razole	Omep-razole	Omeprazole Magnesium	Omeprazole/ Sodium Bicarbonate	Pantop-razole	Rabep-Razole
clopidogrel conversion to its active metabolite through CYP2C19									
Gastric malignancy; a symptomatic response with therapy does not preclude the presence of gastric malignancy	a	a	a	a	a	a	a	a	a
Hypersensitivity and anaphylaxis have been reported with treatment	a	-	-	a	-	-	-	-	-
Hypomagnesemia; consider monitoring magnesium at baseline and periodically with long-term treatment	a	a	a	a	a	a	a	a	a
Methotrexate; concomitant use may elevate and prolong serum methotrexate levels leading to toxicity	a	a	a	a	a	a	-	a	a
Potential interference with toxicology screen for tetrahydrocannabinol	-	-	-	-	-	-	-	a	-
Serum chromogranin A; increased levels due to drug-induced decreases in gastric acidity	-	a	a	-	a	a	-	-	-
Tumorigenicity; rare types of gastrointestinal tumors occurred in rodents with long-term treatment	-	-	-	-	-	-	-	a	-

Drug Interactions

Table 9. Drug Interactions[24-15,28]

Generic Name	Interacting Medication or Disease	Potential Result
Proton pump inhibitors (all)	Azole antifungals	Proton-pump inhibitors may reduce the bioavailability of certain azole antifungals, reducing plasma levels and antifungal activity. Concurrent use should be avoided. If concurrent use is necessary, administer the oral azole antifungal with an acidic beverage.
Proton pump inhibitors (all)	Protease inhibitors	Proton-pump inhibitors may reduce the dissolution of certain protease inhibitors, reducing gastrointestinal absorption and antiviral activity. Saquinavir plasma levels may increase. Dose adjustment of some protease inhibitors may be required with concurrent administration. The use of proton-pump inhibitors with atazanavir is not recommended.
Proton pump inhibitors (all)	Methotrexate	Proton-pump inhibitors coadministered with methotrexate may elevate serum levels of methotrexate or its active metabolite hydroxymethotrexate; however, no formal drug interaction studies have been reported.
Proton pump inhibitors (esomeprazole, omeprazole, pantoprazole and rabeprazole)	Clopidogrel	Proton-pump inhibitors may decrease the antiplatelet activity of clopidogrel by interfering with its metabolic conversion to its active metabolite. If proton-pump inhibitor therapy is clearly indicated, use with caution. A histamine-2 receptor antagonist may be a safer alternative.
Proton pump inhibitors (esomeprazole, omeprazole, pantoprazole and rabeprazole)	Warfarin	Coadministration of certain proton-pump inhibitors and warfarin may result in an increased international normalized ratio and prothrombin time. Monitor patients if concomitant therapy is necessary.
Proton pump inhibitors (dexlansoprazole, lansoprazole and omeprazole)	Tacrolimus	Concomitant administration of certain proton pump inhibitors and tacrolimus may increase tacrolimus levels in patients who are poor metabolizers of cytochrome P450 (CYP) 2C19.
Proton pump inhibitors (esomeprazole and omeprazole)	Cilostazol	Esomeprazole and omeprazole may inhibit the metabolism of cilostazol. A dose decrease of cilostazol to 50 mg twice a day may be required during concurrent administration with omeprazole.
Proton pump inhibitors (esomeprazole and omeprazole)	Strong inducers of CYP2C19 and CYP3A4 (e.g., rifampin)	Coadministration of strong inducers of CYP2C19 or CYP3A4 and esomeprazole or omeprazole may lead to reduced levels of esomeprazole or omeprazole.
Omeprazole	Substrates of CYP2C19	Coadministration of omeprazole with a substrate of CYP2C19 may increase the serum concentration of the substrate.

Dosage and Administration

To maximize efficacy, proton-pump inhibitors (PPIs) should be taken before the first meal of the day.[5-15] If no dosing information is provided for a particular Food and Drug Administration approved indication, the safety and efficacy in children for that particular indication have not been established.

The majority of prescription oral formulations of PPIs have an alternative route of administration. The omeprazole with sodium bicarbonate capsules and the pantoprazole and rabeprazole delayed-release tablets do not have an alternative route of administration; these medications must be administered orally by swallowing the capsules or tablets whole.[5,12,14]

The dexlansoprazole and omeprazole delayed-release capsules can be administered orally; either swallowed whole or sprinkled on applesauce.[10,15] The esomeprazole magnesium and lansoprazole delayed-release capsules and the pantoprazole delayed-release suspension can be administered orally or through a nasogastric tube.[6,8,12] The omeprazole with sodium bicarbonate powder for oral suspension can be administered orally or through a nasogastric or orogastric tube.[14] The esomeprazole magnesium and omeprazole magnesium delayed-release suspension can be administered orally or through a nasogastric or gastric tube.[6,10] The lansoprazole delayed-release disintegrating tablets can be administered orally or through a nasogastric tube or with an oral syringe.[8]

Regarding omeprazole with sodium bicarbonate, two packets of 20 mg are not equivalent to one 40 mg packet; therefore, two 20 mg packets should not be substituted for one 40 mg packet.[17] In addition, two 20 mg capsules are not equivalent to one 40 mg capsule; therefore, two 20 mg capsules should not be substituted for one 40 mg capsule.

Table 10. Dosing and Administration[5-15]

Generic Name	Adult Dose	Pediatric Dose	Availability
Dexlansoprazole	Treatment of symptomatic GERD: Delayed-release capsule: 30 mg QD for four weeks Treatment of erosive esophagitis: Delayed-release capsule: 60 mg QD for up to eight weeks Maintenance of healing of erosive esophagitis: Delayed-release capsule: 30 mg QD*	Safety and efficacy in children have not been established.	Delayed-release capsule: 30 mg 60 mg
Esomeprazole magneisum	Treatment of symptomatic GERD: Delayed-release capsule, delayed-release suspension: 20 mg QD for four weeks† *H pylori* eradication to reduce the risk of duodenal ulcer recurrence: Delayed-release capsule, delayed-release suspension: 40 mg QD for 10 days‡ Treatment of erosive esophagitis: Delayed-release capsule, delayed-release suspension: 20 or 40 mg QD for four to eight weeks§ Maintenance of healing of erosive esophagitis: Delayed-release capsule, delayed-release suspension: 20 mg QD* Treatment of pathological hypersecretory conditions, including	Treatment of symptomatic GERD in children one to 11 years of age: Delayed-release capsule, delayed-release suspension: 10 mg QD for up to eight weeks¶ Treatment of symptomatic GERD in children 12 to 17 years of age: Delayed-release capsule, delayed-release suspension: 20 or 40 mg QD for up to eight weeks Treatment of erosive esophagitis in children one to 11	Delayed-release capsule: 20 mg 40 mg Delayed-release suspension: 2.5 mg 5 mg 10 mg 20 mg 40 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Zollinger-Ellison syndrome: Delayed-release capsule, delayed-release suspension: 40 mg BID‖ Risk reduction of NSAID associated gastric ulcer: Delayed-release capsule, delayed-release suspension: 20 or 40 mg QD for up to six months*	years of age: Delayed-release capsule, delayed-release suspension: 10 or 20 (≥20 kg) mg QD for eight weeks¶ Treatment of erosive esophagitis in children <1 month to 1 year of age: Delayed-release capsule, delayed-release suspension: 2.5 (3 to 5 kg) or 5 (5 to 7.5 kg) or 10 mg (7.5 to 12 kg) QD for six weeks	
Esomeprazole sodium	Treatment of symptomatic GERD#: Solution for injection: 20 or 40 mg QD	Treatment of symptomatic GERD in children 1 month to <1 year of age#: Solution for injection: 0.5 mg/kg QD Treatment of symptomatic GERD in children one year to 17 years of age#: Solution for injection: 10 (<55 kg) or 20 mg (≥55 kg) QD	Solution for injection: 20 mg 40 mg
Lansoprazole	Treatment of symptomatic GERD: Delayed-release capsule, delayed-release disintegrating tablet: 15 mg QD for up to eight weeks *H pylori* eradication to reduce the risk of duodenal ulcer recurrence: Delayed-release capsule, delayed-release disintegrating tablet: 30 mg BID for 10 or 14 days‡ or 30 mg TID for 14 days** Treatment of active duodenal ulcers: Delayed-release capsule, delayed-release disintegrating tablet: 15 mg QD for four weeks Treatment of erosive esophagitis: Delayed-release capsule, delayed-release disintegrating tablet: 30 mg QD for up to eight weeks††	Treatment of symptomatic GERD in children one to 11 years of age: Delayed-release capsule, delayed-release disintegrating tablet: 15 (≤30 kg) or 30 (>30 kg) mg QD for up to 12 weeks¶¶ Treatment of symptomatic GERD in children 12 to 17 years of age: Delayed-release capsule, delayed-release disintegrating tablet: 15 mg QD for up to eight weeks Treatment of erosive	Delayed-release capsule: 15 mg 30 mg Delayed-release capsule (OTC): 15 mg Delayed-release disintegrating tablet: 15 mg 30 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Treatment of active, benign gastric ulcer: Delayed-release capsule, delayed-release disintegrating tablet: 30 mg QD up to eight weeks Healing of NSAID associated gastric ulcer: Delayed-release capsule, delayed-release disintegrating tablet: 30 mg QD for eight weeks‡‡ Maintenance of healing duodenal ulcers: Delayed-release capsule, delayed-release disintegrating tablet: 15 mg QD Maintenance of healing of erosive esophagitis: Delayed-release capsule, delayed-release disintegrating tablet: 15 mg QD Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Delayed-release capsule, delayed-release disintegrating tablet: 60 mg QD§§ Risk reduction of NSAID associated gastric ulcer: Delayed-release capsule, delayed-release disintegrating tablet: 15 mg QD up to 12 weeks‡‡ Treatment of frequent heartburn: Delayed-release capsule (OTC): 15 mg QD for 14 days§§	esophagitis in children one to 11 years of age: Delayed-release capsule, delayed-release disintegrating tablet: 15 (≤30 kg) or 30 (>30 kg) mg QD for up to 12 weeks¶¶ Treatment of erosive esophagitis in children 12 to 17 years of age: Delayed-release capsule, delayed-release disintegrating tablet: 30 mg QD for up to eight weeks	
Omeprazole	Treatment of symptomatic GERD##: Delayed-release capsule: 20 mg QD for four weeks *H pylori* eradication to reduce the risk of duodenal ulcer recurrence: Delayed-release capsule: 20 mg BID for 10 days*** or 40 mg QD for 14 days††† Treatment of active duodenal ulcers: Delayed-release capsule: 20 mg QD for four weeks‡‡‡	Treatment of symptomatic GERD in children 1 to 16 years of age, maintenance of healing of erosive esophagitis in children one to 16 years of age: Delayed-release capsule: 5 (5 to 10 kg), 10 (10 to 20 kg) or 20 (≥20 kg) mg QD	Delayed-release capsule: 10 mg 20 mg 40 mg Delayed-release tablet (OTC): 20 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Treatment of erosive esophagitis[§§§]: Delayed-release capsule: 20 mg QD for four to eight weeks Treatment of active, benign gastric ulcer: Delayed-release capsule: 40 mg QD for four to eight weeks Maintenance of healing of erosive esophagitis: Delayed-release capsule: 20 mg QD[‖‖‖] Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Delayed-release capsule: 60 mg QD[¶¶¶] Treatment of frequent heartburn: Delayed-release tablet (OTC): 20 mg QD for 14 days[§§]		
Omeprazole magnesium	Treatment of symptomatic GERD[##]: Delayed-release capsule: 20 mg QD for four weeks *H pylori* eradication to reduce the risk of duodenal ulcer recurrence: Delayed-release capsule: 20 mg BID for 10 days*** or 40 mg QD for 14 days[†††] Treatment of active duodenal ulcers: Delayed-release capsule: 20 mg QD for four weeks[‡‡‡] Treatment of erosive esophagitis [§§§]: Delayed-release capsule: 20 mg QD for four to eight weeks Treatment of active, benign gastric ulcer: Delayed-release capsule: 40 mg QD for four to eight weeks Maintenance of healing of erosive esophagitis: Delayed-release capsule: 20 mg QD[‖‖‖] Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome:	Treatment of symptomatic GERD in children 1 to 16 years of age, maintenance of healing of erosive esophagitis in children one to 16 years of age: Delayed-release capsule: 5 (5 to 10 kg), 10 (10 to 20 kg) or 20 (≥20 kg) mg QD	Delayed-release capsule (OTC): 20.6 mg Delayed-release tablet (OTC): 20 mg Delayed-release suspension: 2.5 mg 10 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Delayed-release capsule: 60 mg QD[¶¶¶] Treatment of frequent heartburn: Delayed-release tablet (OTC): 20 mg QD for 14 days[§§]		
Omeprazole with sodium bicarbonate	Treatment of symptomatic GERD: Capsule, powder for oral suspension: 20 mg QD for four weeks Treatment of active duodenal ulcers: Capsule, powder for oral suspension: 20 mg QD for four weeks[‡‡‡] Treatment of erosive esophagitis: Capsule, powder for oral suspension: 20 mg QD for 4 to 8 weeks Treatment of active, benign gastric ulcer: Capsule, powder for oral suspension: 40 mg QD for four to eight weeks Maintenance of healing of erosive esophagitis: Capsule, powder for oral suspension: 20 mg once daily Risk reduction of upper gastrointestinal bleeding in critically ill patients: Powder for oral suspension (40 mg/1,680 mg): initial, 40 mg; followed by 40 mg six to eight hours later and 40 mg thereafter for 14 days Treatment of frequent heartburn: Capsule (OTC): 20 mg QD for 14 days	Safety and efficacy in children have not been established.	Capsule: 20 mg 40 mg Capsule (OTC): 20 mg Powder for oral suspension: 20 mg 40 mg
Pantoprazole	Treatment of symptomatic GERD[###]: Solution for injection: 40 mg QD for 7 to 10 days Treatment of erosive esophagitis: Delayed release suspension, delayed-release tablet: 40 mg QD for up to eight weeks[****] Maintenance of healing of erosive esophagitis: Delayed-release suspension, delayed-release tablet: 40 mg QD Treatment of pathological	Treatment of erosive esophagitis in children ≥5 years of age: Delayed-release suspension, delayed-release tablet: 20 (15 to 40 kg) or 40 (≥40 kg) mg QD for up to eight weeks	Delayed-release suspension: 40 mg Delayed-release tablet: 20 mg 40 mg Solution for injection: 40 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	hypersecretory conditions, including Zollinger-Ellison syndrome: Delayed-release suspension, delayed-release tablet: 40 mg BID†††† Solution for injection: 80 mg BID‡‡‡‡		
Rabeprazole	Treatment of symptomatic GERD: Delayed-release tablet: 20 mg QD for four weeks† *H pylori* eradication to reduce the risk of duodenal ulcer recurrence: Delayed-release tablets: 20 mg BID for seven days‡ Treatment of active duodenal ulcers: Delayed-release tablet: 20 mg QD for four weeks§§§§ Treatment of erosive esophagitis: Delayed-release tablet: 20 mg QD for four to eight weeks‖‖‖‖ Maintenance of healing of erosive esophagitis: Delayed-release tablet: 20 mg QD Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Delayed-release tablet: 60 mg QD¶¶¶¶	GERD in children ≥12 years: Delayed-release tablet: 20 mg QD for up to eight weeks	Delayed-release tablet: 20 mg

Drug regimen abbreviations: BID=twice daily, QID=four times daily, TID=three times daily
GERD=gastroesophageal reflux disease, *H pylori=Helicobacter pylori*, NSAID=nonsteroidal anti-inflammatory drug, OTC=over-the-counter
*Studies did not extend beyond six months.
†If symptoms do not resolve completely after four weeks, an additional four weeks of treatment may be considered.
‡As triple therapy with amoxicillin 1,000 mg twice daily plus clarithromycin 500 mg twice daily.
§The majority of patients are healed within four to eight weeks. For patients who do not heal after four to eight weeks, an additional four to eight weeks of treatment may be considered.
‖The dosage of esomeprazole magnesium in patients with pathological hypersecretory conditions varies with the individual patient. Dosage regimens should be adjusted to individual patient needs. Doses up to 240 mg/day have been administered.
¶Doses >1 mg/kg/day have not been studied.
#Indicated for the short-term treatment of gastroesophageal reflux disease in patients with a history of erosive esophagitis as an alternative to oral therapy in patients when esomeprazole magnesium delayed-release capsules is not possible or appropriate.
**As combination therapy with amoxicillin 1,000 mg three times daily.
††For patients who do not heal with lansoprazole for eight weeks (5 to 10%), it may be helpful to give an additional eight weeks of treatment. If there is a recurrence of erosive esophagitis, an additional eight-week course of lansoprazole may be considered.
‡‡Controlled studies did not extend beyond indicated duration.
§§A 14-day course every four months may be considered if required.
‖‖Varies with individual patient. Recommended adult starting dose is 60 mg once daily. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosages up to 90 mg twice daily have been administered. Daily doses of greater than 120 mg should be administered in divided doses. Some patients with Zollinger-Ellison Syndrome have been treated continuously with lansoprazole for more than four years.
¶¶The lansoprazole dose was increased (up to 30 mg twice daily) in some pediatric patients after two or more weeks of treatment if they remained symptomatic.
##The efficacy of omeprazole used for longer than eight weeks in these patients has not been established. If a patient does not respond to eight weeks of treatment, an additional four weeks of treatment may be given. If there is recurrence of gastroesophageal reflux disease, additional four to eight week courses of omeprazole may be considered.

***As triple therapy with amoxicillin 1,000 mg twice daily plus clarithromycin 500 mg twice daily. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.
†††As combination therapy with clarithromycin 500 mg three times daily. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.
‡‡‡Most patients heal within 4 weeks. Some patients may require an additional four weeks of therapy.
§§§Diagnosed by endoscopy. The efficacy of omeprazole used for longer than eight weeks in these patients has not been established. If a patient does not respond to eight weeks of treatment, an additional four weeks of treatment may be given. If there is recurrence of erosive esophagitis, additional four to eight week courses of omeprazole may be considered.
‖‖‖Controlled studies did not extend beyond 12 months.
¶¶¶Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg three times daily have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with omeprazole for more than five years.
###Indicated for treatment in patients with gastroesophageal reflux disease associated with a history of erosive esophagitis. Safety and efficacy for more than 10 days have not been demonstrated.
****For adult patients who have not healed after eight weeks of treatment, an additional eight-week course of pantoprazole may be considered.
††††Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg/day have been administered.
‡‡‡‡The frequency of dosing can be adjusted to individual patient needs based on acid output measurements. Daily doses higher than 240 mg or administered more than six days have not been studied.
§§§§Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.
‖‖‖‖For those patients who have not healed after eight weeks of treatment, an additional eight week course of rabeprazole may be considered.
¶¶¶¶Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg once daily and 60 mg twice daily have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with rabeprazole for up to one year.

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Gastroenterology: **Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease (2005)**[17]	· Antacids and over-the-counter (OTC) acid suppressants are options for patient-directed therapy for heartburn and regurgitation. Patients should be evaluated if symptoms persist and they require continuous therapy. · Cimetidine, famotidine, nizatidine and ranitidine are available OTC in doses that have been shown to decrease gastric acid, particularly after a meal. While there are some differences in potency, duration and rapidity of action, they may be generally used interchangeably. · Acid suppression is the mainstay of gastroesophageal reflux disease (GERD) therapy and proton-pump inhibitors (PPIs) provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients. Although less effective than PPIs, histamine H_2-receptor antagonists (H_2RAs) given in divided doses may be effective in some patients with less severe GERD. · Based on randomized trials in over 3,000 patients with erosive esophagitis, symptomatic relief can be expected in 27% of placebo-treated, 60% of H_2RA-treated and 83% of PPI-treated patients. Esophagitis healed in 24% of placebo-treated, 50% of H_2RA-treated and 78% of PPI-treated patients. Both higher doses and more frequent dosing of H_2RAs appear to improve results in the treatment of reflux, but are still inferior to PPIs. · Continuous therapy to control symptoms and prevent complications is appropriate since GERD is a chronic condition.
American Gastroenterological Association: **Medical Position Statement on the Management of**	· Antisecretory drugs are recommended for the treatment of patients with esophageal GERD syndromes (healing esophagitis and symptomatic relief). In these conditions, PPIs are more effective than H_2RAs, which are more effective than placebo. · Twice-daily PPI therapy is recommended for patients who had an inadequate symptom response to once-daily PPI therapy. There is no

Clinical Guideline	Recommendations
Gastroesophageal Reflux Disease (2008)[18]	evidence of improved efficacy by adding a nocturnal dose of an H_2RA to twice-daily PPI therapy. · A short course or as needed use of antisecretory drugs is recommended in patients with a symptomatic esophageal syndrome without esophagitis when symptom control is the primary objective. For a short course of therapy, PPIs are more effective than H_2RAs, which are more effective than placebo. · Circumstances in which one antisecretory drug might be preferable to another primarily relate to side effects or onset of effect. The most common side effects of PPIs are abdominal pain, constipation, diarrhea and headache, which can usually be circumvented by switching among alternative PPIs or lowering the PPI dose. Medications taken in response to symptoms should be rapidly acting. The most rapidly acting agents are antacids, the efficacy of which can be sustained by combining them with a PPI or H_2RA. · Long-term use of PPIs is recommended for the treatment of patients with esophagitis once they are proven clinically effective. Long-term therapy should be titrated down to the lowest effective dose based on symptom control. On-demand therapy is a reasonable strategy in patients with an esophageal GERD syndrome without esophagitis, where symptom control is the primary objective. · Less than daily dosing of PPI therapy as maintenance therapy is not recommended in patients with an esophageal syndrome who previously had erosive esophagitis.
American College of Gastroenterology: **Guidelines for the Management of Dyspepsia (2005)**[19]	· Empiric trial with a PPI for four to eight weeks as an initial therapy option is recommended in dyspeptic patients ≤55 years old without alarm features (e.g., bleeding, dysphagia, family history of gastrointestinal cancer, weight loss) and where *Helicobacter pylori* (*H pylori*) prevalence is low (<10%). · If initial acid suppression fails after two to four weeks, it is reasonable to consider changing drug class or dosing. In patients who respond to initial therapy, stop treatment after four to eight weeks; if symptoms recur, another course of the same treatment is justified. · In populations with a moderate to high prevalence of *H pylori* infection (≥10%), test and treat for *H pylori* and give a trial of acid suppression if eradication is successful but symptoms do not resolve. · Dyspeptic patients >55 years old or who have alarm features should undergo prompt esophagogastroduodenoscopy to rule out peptic ulcer disease, esophagogastric malignancy and other upper gastrointestinal diseases.
American Gastroenterological Association: **Medical Position Statement: Evaluation of Dyspepsia (2005)**[20]	· Patients with dyspepsia (without GERD or nonsteroidal anti-inflammatory drugs [NSAIDS]) who are ≤55 years old and do not have any alarm features should receive *H pylori* testing and treatment of positive cases followed by acid suppression if symptoms remain. PPIs are the drug class of choice for acid suppression. · Patients who are *H pylori* negative should be prescribed an empirical trial of acid suppression with a PPI for four to eight weeks. · Empirical PPI therapy is the most cost-effective approach in populations with a low prevalence of *H pylori* (≤10%). · Patients with dyspepsia who are >55 years old or who have alarm features should have an esophagogastroduodenoscopy with biopsy for *H pylori*. Treatment should be targeted at the underlying diagnosis.
American College of Gastroenterology:	· In the United States, the recommended primary therapies for *H pylori* infection include a PPI, clarithromycin and amoxicillin or metronidazole

Clinical Guideline	Recommendations
Guideline on the Management of *Helicobacter pylori* Infection (2007)[21]	(clarithromycin-based triple therapy) for 14 days for eradication rates of 70 to 85% or a PPI or H_2RA, bismuth, metronidazole and tetracycline (bismuth-based quadruple therapy) for 10 to 14 days for eradication rates of 75 to 90%. · The currently available PPIs perform comparably when used in the triple therapy regimens. A meta-analysis of 13 studies suggests that twice daily dosing of a PPI (lansoprazole, omeprazole, pantoprazole and rabeprazole) in clarithromycin-based triple regimens is more effective than once- daily dosing. · Sequential therapy consisting of a PPI and amoxicillin for five days followed by a PPI, clarithromycin and tinidazole for an additional five days may provide an alternative to clarithromycin-based triple or bismuth-based quadruple therapy but requires validation within the United States before it can be recommended as a first-line therapy. · In patients with persistent *H pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient. Bismuth-based quadruple therapy for seven to 14 days is an accepted salvage therapy. Levofloxacin-based triple therapy for 10 days is another option for patients with persistent infection but this regimen requires validation in the United States.
European *Helicobacter pylori* Study Group: **Current Concepts in the Management of *Helicobacter pylori* Infection–The Maastricht III Consensus Report (2007)**[22]	· Recommended first-line treatment is a PPI, clarithromycin and amoxicillin or metronidazole in populations with less than 15 to 20% clarithromycin resistance. In populations with less than 40% metronidazole resistance a regimen containing a PPI, clarithromycin and metronidazole is preferable. A 14-day treatment regimen is 12% more effective than a seven-day regimen. A seven-day treatment regimen may be acceptable where local studies show that it is effective. · Bismuth-based quadruple therapies (10 or 14 days) are alternative first-choice treatments. · Bismuth-based quadruple therapies remain the best second-choice treatment. If not available, a PPI, amoxicillin or tetracycline and metronidazole are recommended.
American College of Gastroenterology: **Updated Guidelines 2008 for the Diagnosis, Surveillance and Therapy of Barrett's Esophagus (2008)**[25]	· Barrett's esophagus is believed to be the major risk factor for the development of esophageal adenocarcinoma. The incidence of adenocarcinoma of the esophagus continues to rise rapidly. · Barrett's esophagus is a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus. · Screening for Barrett's esophagus remains controversial because of the lack of documented impact on mortality from esophageal adenocarcinoma. · The grade of dysplasia determines the appropriate surveillance interval. Any grade dysplasia by histology should be confirmed by an expert pathologist. · Low-grade dysplasia requires expert pathologist confirmation and more frequent endoscopy and biopsy. · High-grade dysplasia also requires confirmation by an expert pathologist and represents a threshold for intervention. A more intensive biopsy protocol is necessary to exclude the presence of concomitant adenocarcinoma. · Any mucosal irregularity (e.g., nodularity, ulcer) is best assessed with endoscopic resection for a more extensive histologic evaluation and exclusion of cancer.

Clinical Guideline	Recommendations
	· Management of patients with high-grade dysplasia is dependent on local expertise, both endoscopic and surgical and the patient's age, comorbidity and preferences. · No biomarkers or panel is currently ready for routine clinical use. · Chemoprevention represents a promising future strategy. · The goal of pharmacologic acid suppression with agents such as PPIs is to control reflux symptoms. · Reflux symptoms can be controlled in most patients with PPI therapy; twice daily dosing may be necessary in a subgroup of patients. · There is currently no data that directly support the use of high dose antisecretory therapy to delay or prevent the development of esophageal adenocarcinoma. · Patients who are optimal candidates for surgery may elect fundoplication, including patients lacking a major comorbidity and whose reflux symptoms are controlled with PPI therapy. · The vast majority of data do not provide support that fundoplication prevents esophageal adenocarcinoma.
American Gastroenterological Association: **Medical Position Statement on the Management of Barrett's Esophagus (2011)**[26]	· Patients with multiple risk factors associated with esophageal adenocarcinoma (age 50 years or older, male sex, white race, chronic GERD, hiatal hernia, elevated body mass index, and intra-abdominal distribution of body fat) should be screened for Barrett's esophagus. · Endoscopic surveillance should be performed in patients with Barrett's esophagus at the following intervals: no dysplasia: three to five years, low-grade dysplasia: 6 to 12 months, high-grade dysplasia in the absence of eradication therapy: three months. · For patients with Barrett's esophagus who are undergoing surveillance, an endoscopic evaluation should be performed using white light endoscopy and four-quadrant biopsy specimens be taken every 2 cm. Four-quadrant biopsy specimens should be obtained every 1 cm in patients with known or suspected dysplasia. · Specific biopsy specimens of any mucosal irregularities should be submitted separately to the pathologist. · Requiring chromoendoscopy or advanced imaging techniques for the routine surveillance of patients with Barrett's esophagus is not needed. · Attempts to eliminate esophageal acid exposure (PPIs in doses greater than once daily, esophageal pH monitoring to titrate PPI dosing, or antireflux surgery) for the prevention of esophageal adenocarcinoma is not recommended. · Patients should be screened to identify cardiovascular risk factors for which aspirin therapy is indicated. Aspirin solely to prevent esophageal adenocarcinoma in the absence of other indications is not recommended. · Endoscopic eradication therapy with radiofrequency ablation, photodynamic therapy or endoscopic mucosal resection is recommended in patients with confirmed high-grade dysplasia within Barrett's esophagus rather than surveillance. · Endoscopic mucosal resection is recommended for patients who have dysplasia in Barrett's esophagus associated with a visible mucosal irregularity to determine the T stage of the neoplasia.
American College of Gastroenterology: **Guidelines for Prevention of Nonsteroidal Anti-**	· Patients requiring nonsteroidal anti-inflammatory drug (NSAID) therapy who are at high risk (e.g., prior ulcer bleeding) should receive alternative therapy, or if anti-inflammatory treatment is necessary, a cyclooxygenase (COX)-2 inhibitor, and co-therapy with misoprostol or high-dose PPI. · Patients at moderate risk can be treated with a COX-2 inhibitor alone or

Clinical Guideline	Recommendations
inflammatory Drugs- Related Ulcer Complications (2009)[23]	with a traditional nonselective NSAID plus misoprostol or a PPI. · Patients at low risk can be treated with a nonselective NSAID. · Patients for whom anti-inflammatory analgesics are recommended who also require low-dose aspirin therapy for cardiovascular disease can be treated with naproxen plus misoprostol or a PPI. · Patients at moderate gastrointestinal risk who are also at high cardiovascular risk should be treated with naproxen plus misoprostol or a PPI. Patients at high gastrointestinal and high cardiovascular risk should avoid using NSAIDS or COX-2 inhibitors. Alternative therapy should be prescribed. · High-dose H_2RAs are more effective than placebo in reducing the risk of NSAID-induced endoscopic peptic ulcers; however, the H_2RAs are significantly less effective than PPIs.
American College of Gastroenterology: **Management of Patients With Ulcer Bleeding (2012)**[24]	· Immediately assess hemodynamic status upon presentation and begin resuscitative measures as needed. · Blood transfusions should target hemoglobin ≥7 g/dL, with higher hemoglobin targeted in patients with intravascular volume depletion or comorbidities. · Discharge from the emergency department without endoscopy may be considered for patients with urea nitrogen <18.2 mg /dL, hemoglobin ≥13.0 g/dL for men (12.0 g/dL for women), systolic blood pressure ≥110 mm Hg; pulse <100 beats/min; and without evidence of melena, syncope, cardiac failure, and liver disease. · Consider administering intravenous erythromycin (250 mg ~30 min before endoscopy) to improve diagnostic yield and decrease the need for repeat endoscopy, although erythromycin has not consistently demonstrated improved clinical outcomes. · Pre-endoscopic intravenous PPI (e.g., 80 mg bolus followed by 8 mg/hour infusion) may be considered to decrease the proportion of patients who have higher risk stigmata of hemorrhage at endoscopy and who receive endoscopic therapy. The PPIs have not demonstrated improved clinical outcomes with regard to further bleeding, surgery or death. · If endoscopy is delayed or cannot be performed, administer intravenous PPI to reduce further bleeding. · Following endoscopic hemostasis, intravenous PPI therapy with 80 mg bolus followed by 8 mg/hour continuous infusion for 72 hours should be given to patients who have an ulcer with active bleeding, a non-bleeding visible vessel or an adherent clot. · Patients with flat-pigmented ulcer spots or clean bases can receive standard PPI therapy (e.g., oral PPI once daily). · Patients with clean-based ulcers may receive a regular diet and be discharged following endoscopy if they are hemodynamically stable, their hemoglobin is stable, no other medical problems, and they have a residence where they can be observed. · Patients with *H. pylori*-associated bleeding ulcers should receive *H. pylori* therapy. After eradication is documented, maintenance antisecretory therapy is not necessary unless the patient requires NSAIDs or antithrombotics. · Carefully assess and evaluate the need for continued NSAID therapy in patients with NSAID-induced ulcers. In patients who must resume NSAIDs, a COX-2 selective NSAID at the lowest effective dose plus daily PPI is recommended. · Assess the need for aspirin in patients with low-dose aspirin-induced

Clinical Guideline	Recommendations
	bleeding ulcers. If given for secondary prevention (i.e., established cardiovascular disease), aspirin should be resumed as soon as possible after bleeding ceases in most patients. Long-term daily PPI therapy should also be provided. If given for primary prevention (i.e., no established cardiovascular disease), anti-platelet therapy likely should not be resumed in most patients. · In patients with idiopathic (non-*H. pylori*, non-NSAID) ulcers, long-term antiulcer therapy (e.g., daily PPI) is recommended.

Conclusions

Proton-pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion available.[1] All of the PPIs are Food and Drug Administration (FDA)-approved for the treatment and maintenance of gastroesophageal reflux disease (GERD) and, with the exception of dexlansoprazole, for the treatment of pathological hypersecretory conditions.[4-15,28] With the exception of dexlansoprazole, esomeprazole sodium, omeprazole with sodium bicarbonate and pantoprazole, all of the PPIs are approved for the eradication of *Helicobacter pylori* (*H pylori)* to reduce the risk of duodenal ulcer recurrence. Dexlansoprazole, esomeprazole sodium and omeprazole with sodium bicarbonate are the only PPIs that are not FDA-approved for use in children. All PPIs are available in delayed-release oral formulations, with the exception of esomeprazole sodium, and can be dosed once daily. Dexlansoprazole is uniquely formulated to release at different time intervals, at two different sites of the small intestine. The clinical significance of this is unknown. Esomeprazole magnesium, omeprazole magnesium and pantoprazole are the PPIs also available in a delayed-release oral suspension. Omeprazole, omeprazole magnesium and omeprazole with sodium bicarbonate are also available in over-the-counter formulations. Esomeprazole sodium and pantoprazole are available in intravenous formulations for short-term use in patients unable to take medications by mouth. Lansoprazole, omeprazole, omeprazole with sodium bicarbonate and pantoprazole are all available generically.

Current medical evidence has demonstrated that PPI therapy is highly effective in treating, providing symptomatic relief and preventing relapse in gastric acid disorders such as erosive esophagitis and symptomatic GERD.[29-66] In meta-analyses and direct comparator trials lansoprazole, omeprazole, pantoprazole and rabeprazole all demonstrated comparable healing rates, maintenance of healing or symptomatic relief of GERD.[30,32,40,42,46,48,51,52] A few trials reported statistically faster and greater symptomatic relief with lansoprazole compared to omeprazole; however, the significance of these differences in clinical practice is not known.[57] There is evidence through meta-analyses and several clinical trials that esomeprazole provides higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole and pantoprazole.[30, 32,40,42-44,48,51,52] Subgroup analyses in a few trials noted better healing rates with esomeprazole in patients with more severe disease.[49,51] Close analysis of all of these trials show that the overall differences were generally small. Though the results are statistically significant, the clinical significance of these differences is not known. The results of these trials have not been replicated consistently in other trials, particularly in trials with lansoprazole and pantoprazole.[39,41,47,50,53,55] It should be noted that most trials that compared esomeprazole to omeprazole employed doses of 40 mg for esomeprazole and 20 mg for omeprazole.[30,32,46,48] Since esomeprazole is a stereoisomer of omeprazole, comparing 40 mg of esomeprazole to 20 mg of omeprazole is comparable to evaluating a double dose of omeprazole to a single dose of omeprazole. A 2007 Cochrane review concluded that there was no major difference in efficacy among the currently available PPIs for the short-term management of reflux esophagitis when administered in equivalent dosages.[87] Currently, there are no trials directly comparing the different omeprazole formulations to one another. Additionally, there is a lack of head-to-head studies of dexlansoprazole with the other agents in this class.

Clinical studies have demonstrated that PPIs are also highly effective in the treatment of peptic ulcer disease caused by chronic nonsteroidal anti-inflammatory drug (NSAID) therapy or *H pylori* infection when coupled with antibiotics.[66-78] Meta-analyses and head-to-head trials comparing PPIs to each other have shown comparable rates of eradication when administered at comparable doses and paired with

comparable antibiotic regimens. One small trial reported higher eradication rates for patients treated with esomeprazole than pantoprazole.[72] A few studies have noted higher eradication rates of *H pylori* in patients who were poor metabolizers of PPIs.[3,27] Additional studies are needed before definitive conclusions can be made regarding the use of certain PPIs in specific patient populations.

Current consensus among various national and international treatment guidelines recommend a PPI as the first-line therapy in the treatment and maintenance of healed erosive esophagitis, symptomatic GERD, dyspepsia (patients ≤55 years and no alarm features), and peptic ulcer disease caused by NSAID therapy.[17-20, 23,24] Triple and quadruple combination therapy with antibiotics and a PPI are considered first-line therapy for peptic ulcer disease caused by *H pylori.*[21-22] None of the treatment guidelines recommend one PPI over another or one formulation of a PPI over another.[17-26]

Comparative data regarding the PPIs has not demonstrated distinct, clinically significant differences regarding safety and tolerability. Overall, no one PPI offers a significant clinical advantage over another. Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in this class and offer no significant clinical advantage over other alternatives in general use.

References

1. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology. 2000;118(2 Suppl 1):S9-31.
2. Welage LS. Pharmacologic features of proton-pump inhibitors and their potential relevance to clinical practice. Gastroenterol Clin North Am. 2003;32(3 Suppl):S25-35.
3. Wolfe MM. Overview and comparison of the proton-pump inhibitors for the treatment of acid-related disorders. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Sept 12]. Available from: http://www.utdol.com/online/content/topic.do?topicKey=acidpep/10094&selectedTitle=1~150&source=search_result.
4. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2012 [cited 2012 Sept 12]. Available from: http://online.factsandcomparisons.com.
5. Aciphex® [package insert].Woodcliff Lake (NJ): Eisai Inc.; 2012 May.
6. Nexium® [package insert]. Wilmington (DE): AstraZeneca LP; 2012 Jan.
7. Nexium® IV [package insert]. Wilmington (DE): AstraZeneca LP; 2012 Jan.
8. Prevacid® [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2012 May.
9. Prevacid® OTC [product label]. Basal (Switzerland): Novartis Consumer Health, Inc.; 2009 Aug.
10. Prilosec® [package insert]. Wilmington (DE): AstraZeneca LP; 2012 Feb.
11. Prilosec® OTC [product label]. Cincinnati (OH): Procter and Gamble; 2011 Aug.
12. Protonix® [package insert]. Philadelphia (PA): Wyeth Pharmaceuticals Inc.; 2012 May.
13. Protonix® IV [package insert].Philadelphia (PA): Wyeth Pharmaceuticals Inc.; 2012 May.
14. Zegerid® [package insert]. San Diego (CA): Santarus Inc.; 2011 May.
15. Dexilant® [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2012 May.
16. Kapidex® (dexlansoprazole) renamed Dexilant® in U.S. to avoid name confusion [press release on the internet]. Takeda Pharmaceuticals North America, Inc. 2010 Mar 4 [cited 2012 Sep 12]. Available from: http://www.takeda.us/newsroom/press_release_detail.aspx?year=2010&id=114.
17. DeVault KR, Castell DO; American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 2005;100(1):190-200.
18. Kahrilas PJ, Shaheen NJ, Vaezi MF, Hiltz SW, Black E, Modlin IM, et al; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology. 2008 Oct;135(4):1383-91,1391.e1-5.
19. Talley NJ, Vakil N; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005;100(10):2324-37.
20. Talley NJ; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement: Evaluation of dyspepsia. Gastroenterology. 2005 Nov;129(5):1753-5.
21. Chey WD, Wong BCY and the Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology Guideline on the management of Helicobacter pylori infection. Am J Gastroenterol. 2007;102:1808-25.
22. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al and the European Helicobacter Study Group (EHSG). Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut. 2007;56(6):772-81.
23. Lanza FL, Chan FKL, Quigley EMM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728-38.
24. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012 Mar;107(3):345-60.
25. Wang K, Sampliner RE. Practice Guidelines: Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol. 2008;103:788-97.
26. American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011 Mar;140(3):1084-91.
27. Fock KM, Ang TL, Bee LC, Lee EJ. Proton-pump inhibitors: do differences in pharmacokinetics translate into differences in clinical outcomes? Clin Pharmacokinet. 2008;47(1):1-6.

28. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2012 [cited 2012 Sept 12]. Available from: http://www.thomsonhc.com/.
29. van Pinxteren B, Sigterman KE, Bonis P, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2010 Nov 10;(11):CD002095.
30. Klok RM, Postma MJ, van Hout BA, Brouwers JR. Meta-analysis: comparing the efficacy of proton-pump inhibitors in short-term use. Aliment Pharmacol Ther. 2003;17(10):1237-45.
31. Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared to omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. Clin Ther. 2001;23(7):998-1017.
32. Edwards SJ, Lind T, Lundell L. Systematic review of proton-pump inhibitors for the acute treatment of reflux oesophagitis. Aliment Pharmacol Ther. 2001;15(11):1729-36.
33. Fass R, Inadomi J, Han C, Mody R, O'Neil J, Perez MC. Maintenance of heartburn relief after step-down from twice-daily proton pump inhibitor to once-daily dexlansoprazole modified release. Clin Gastroenterol Hepatol. 2012 Mar;10(3):247-53.
34. Fass R, Johnson DA, Orr WC, Han C, Mody R, Stern KN, et al. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. Am J Gastroenterol. 2011 Mar;106(3):421-31.
35. Howden CW, Larsen LM, Perez MC, Palmer R, Atkinson SN. Clinical trial: efficacy and safety of dexlansoprazole MR 60 mg and 90 mg in healed erosive oesophagitis – maintenance of healing and symptom relief. Aliment Pharmacol Ther. 2009;30:895-907.
36. Metz DC, Howden CW, Perez MC, Larsen L, O'Neil J, Atkinson SN. Clinical trial dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive esophagitis. Aliment Pharmacol Ther. 2009;29:742-54.
37. Fass R, Chey WD, Zakko SF, Andhivarothais N, Palmers RN, Perez MC et al. Clinical trial: the effect of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. Aliment Pharmacol Ther. 2009;29:1261-72.
38. Sharma P, Shaheen NJ, Perez MC, Pilmer BL, Lee M, Atkinson SN, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation – results from two randomized controlled studies. Aliment Pharmacol Ther. 2009;29:731-41.
39. Chey W, Huang B. Jackson RL. Lansoprazole and esomeprazole in symptomatic GERD: a double-blind, randomized, multicentre trial in 3000 patients confirms comparable symptom relief. Oesophagitis. Clin Drug Invest .2003;23(2):69-84.
40. Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S, et al. Esomeprazole (40 mg) compared to lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002;97:575-83.
41. Howden CW, Ballard EDI, Robieson W. Evidence for therapeutic equivalence of lansoprazole 30 mg and esomeprazole 40 mg in the treatment of erosive oesophagitis. Clin Drug Invest. 2002;22(2):99-109.
42. Devault KR, Johanson JF, Johnson DA, Liu S, Sostek MB. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. Clin Gastroenterol Hepatol. 2006 Jul;4(7):852-9.
43. Fennerty MB, Johanson JF, Hwang C, Sostek M. Efficacy of esomeprazole 40 mg vs lansoprazole 30 mg for healing moderate-to-severe erosive oesophagitis. Aliment Pharmacol Ther. 2005;21(4):455-63.
44. Lauritsen K, Devière J, Bigard MA, Bayerdörffer E, Mózsik G, Murray F, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther. 2003;17(3):333-41.
45. Tsai HH, Chapman R, Shepherd A, McKeith D, Anderson M, Vearer D, et al. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term

maintenance of endoscopy-negative gastro-oesophageal reflux patients: the COMMAND Study. Aliment Pharmacol Ther. 2004;20:657-65.
46. Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, et al. Efficacy and safety of esomeprazole compared to omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol. 2001;96:656-65.
47. Armstrong D, Talley NJ, Lauritsen K, Moum B, Lind T, Tunturi-Hihnala H, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. Aliment Pharmacol Ther. 2004;20(4):413-21.
48. Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, et al. Esomeprazole improves healing and symptom resolution as compared to omeprazole in reflux oesophagitis patients: a randomized controlled trial. Aliment Pharmacol Ther. 2000;14:1249-58.
49. Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci. 2006 May;51(5):844-50.
50. Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci. 2006 May;51(5):852-7.
51. Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, et al. A randomized comparative study of esomeprazole 40 mg vs pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther. 2005;21(6):739-46.
52. Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, et al. Esomeprazole 20 mg vs pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. Aliment Pharmacol Ther. 2005 Nov 1;22(9):803-11.
53. Scholten T, Gatz G, Hole U. Once-daily pantoprazole 40 mg and esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. Aliment Pharmacol Ther. 2003;18(6):587-94.
54. Glatzel D, Abdel-Qader M, Gatz G, Pfaffenberger B. Pantoprazole 40 mg is as effective as esomeprazole 40 mg to relieve symptoms of gastroesophageal reflux disease after 4 weeks of treatment and superior regarding the prevention of symptomatic relapse. Digestion. 2007;75(Suppl 1):69-78.
55. Goh KL, Benamouzig R, Sander P, Schwan T; EMANCIPATE. Efficacy of pantoprazole 20 mg daily compared to esomeprazole 20 mg daily in the maintenance of healed gastroesophageal reflux disease: a randomized, double-blind comparative trial-the EMANCIPATE study. Eur J Gastroenterol Hepatol. 2007;19(3):205-11.
56. 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(2):227-31.
57. Richter JE, Kahrilas PJ, Sontag SJ, Kovacs TO, Huang B, Pencyla JL. Comparing lansoprazole and omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients. Am J Gastroenterol. 2001;96:3089-98.
58. Pilotto A, Franceschi M, Leandro G, Scarcelli C, D'Ambrosio LP, Paris F, et al. Comparison of four proton-pump inhibitors for the short-term treatment of esophagitis in elderly patients. World J Gastroenterol. 2007;13(33):4467-72.
59. Pouchain D, Bigard MA, Liard F, Childs M, Decaudin A, McVey D. Gaviscon® vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. a direct comparative randomised trial. BMC Gastroenterol. 2012 Feb 23;12:18.
60. Bardhan KD, Van Rensburg C. Comparable clinical efficacy and tolerability of 20 mg pantoprazole and 20 mg omeprazole in patients with grade I reflux oesophagitis. Aliment Pharmacol Ther. 2001;15:1585-91.
61. 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.
62. Pace F, Annese V, Prada A, Zambelli A, Casalini S, Nardini P, et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomized, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux

oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Dig Liver Dis. 2005;37:741-50.
63. Mönnikes H, Schwan T, van Rensburg C, Straszak A, Theek C, Sander P, et al. Randomised clinical trial: sustained response to PPI treatment of symptoms resembling functional dyspepsia and irritable bowel syndrome in patients suffering from an overlap with erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2012 Jun;35(11):1279-89.
64. Fujimoto K, Hongo M; Maintenance Study Group. Safety and efficacy of long-term maintenance therapy with oral dose of rabeprazole 10 mg once daily in Japanese patients with reflux esophagitis. Intern Med. 2011;50(3):179-88.
65. Kinoshita Y, Ashida K, Hongo M; Japan. Rabeprazole Study Group for NERD. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. Aliment Pharmacol Ther. 2011 Jan;33(2):213-24.
66. Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C, et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs. esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther. 2011 Jan;33(2):203-12.
67. Choi HS, Park DI, Hwang SJ, Park JS, Kim HJ, Cho YK, et al. Double-dose, new-generation proton-pump inhibitors do not improve eradication rate. Helicobacter. 2007; 2(6):638-42.
68. Vergara M, Vallve M, Gisbert JP, Calvet X. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003;18:647-54.
69. Ulmer HJ, Beckerling A, Gatz G. Recent use of proton-pump inhibitor-based triple therapies for the eradication of H pylori: a broad data review. Helicobacter. 2003;8(2):95-104.
70. Gisbert JP, Pajares JM. Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis. Dig Liver Dis. 2004;36(4)253-9.
71. Wang X, Fang JY, Lu R, Sun DF. A meta-analysis: comparison of esomeprazole and other proton-pump inhibitors in eradicating Helicobacter pylori. Digestion. 2006;73(2-3):178-86.
72. Hsu PI, Lai KH, Lin CK, Chen WC, Yu HC, Cheng JS, et al. A prospective randomized trial of esomeprazole-vs pantoprazole-based triple therapy for Helicobacter pylori eradication. Am J Gastroenterol. 2005;100(11):2387-92.
73. Wu IC, Wu DC, Hsu PI, Lu CY, Yu FJ, Wang TE, et al. Rabeprazole- vs esomeprazole-based eradication regimens for H pylori infection. Helicobacter. 2007;12(6):633-7.
74. Bazzoli F, Pozzato P, Zagari M, Fossi S, Ricciardiello L, Nicolini G, et al. Efficacy of lansoprazole in eradicating Helicobacter pylori: a meta-analysis. Helicobacter. 1998;3(3):195-201.
75. Gisbert JP, Khorrami S, Calvet X, Pajares JM. Pantoprazole-based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2004;16(1):89-99.
76. Felga G, Silva FM, Barbuti RC, Navarro-Rodriguez T, Zaterka S, Eisig JN. Clarithromycin-based triple therapy for Helicobacter pylori treatment in peptic ulcer patients. J Infect Dev Ctries. 2010 Nov 24;4(11):712-6.
77. McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. Aliment Pharmacol Ther. 2012 Sep;36(5):414-25.
78. Gisbert JP, Khorrami S, Calvet X, Pajares JM. Systematic review: rabeprazole-based therapies in Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003;17(6):751-64.
79. Scheiman JM, Devereaux PJ, Herlitz J, Katelaris PH, Lanas A, Veldhuyzen van Zanten S, et al. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). Heart. 2011 May;97(10):797-802.
80. Ramdani A, Mignon M, Samoyeau R. Effect of pantoprazole vs other proton-pump inhibitors on 24-hour intragastric pH and basal acid output in Zollinger-Ellison syndrome. Gastroenterol Clin Biol. 2002;26(4):355-9.
81. Sugano K, Matsumoto Y, Itabashi T, Abe S, Sakaki N, Ashida K, et al. Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of

a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. J Gastroenterol. 2011 Jun;46(6):724-35.
82. Conrad SA, Gabrielli A, Margolis B, Quartin A, Hata JS, Frank WO, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension vs intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. Crit Care Med. 2005;33(4):760-5.
83. Katz PO, Koch FK, Ballard ED, Bagin RG, Gautille TC, Checani GC, et al. Comparison of the effects of immediate-release omeprazole oral suspension, delayed-release lansoprazole capsules and delayed-release esomeprazole capsules on nocturnal gastric acidity after bedtime dosing in patients with nighttime GERD symptoms. Aliment Pharmacol Ther. 2007 Jan 15;25(2):197-205.
84. Castell D, Bagin R, Goldlust B, Major J, Hepburn B. Comparison of the effects of immediate-release omeprazole powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in patients with symptomatic gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2005;21(12):1467-74.
85. Regula J, Butruk E, Dekkers CP, de Boer SY, Raps D, Simon L, et al. Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole vs omeprazole. Am J Gastroenterol. 2006 Aug;101(8):1747-55.
86. Chan FKL, Lanas A, Scheiman J, Berger M, Nguyen H, Goldstein JL. Celecoxib vs omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet. 2010;376:173-9.
87. Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short-term management of reflux oesophagitis. Cochrane Database Sys Rev. 2007;(2):CD003244.
88. Nelson W, Vermeulen L, Geurkink E, Ehlert D, Reichelderfer M. Clinical and humanistic outcomes in patients with gastroesophageal reflux disease converted from omeprazole to lansoprazole. Arch Intern Med. 2000;160:2491-6.
89. Cote GA, Ferreira MR, Rozenberg-Ben-Dror K, Howden CW. Programme of stepping down from twice daily proton-pump inhibitor therapy for symptomatic gastrooesophageal reflux disease associated with a formulary change at a VA medical center. Aliment Pharmacol Ther. 2007 Mar 15; 25(6):709-14.
90. Meineche-Schmidt V. Empiric treatment with high and standard dose of omeprazole in general practice: two-week randomized placebo-controlled trial and 12-month follow-up of health-care consumption. Am J Gastroenterol. 2004;99(6):1050-8.
91. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton-pump inhibitors and risk of osteoporosis-related fractures. CMAJ. 2008;179(4):319-26.