



## Department of Vermont Health Access

### *Therapeutic Class Review Proton Pump Inhibitors Single Entity Agents*

#### **Overview/Summary**

Proton-pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally recognized as the most potent acid suppressants available.<sup>1</sup> 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 ( $H^+K^+$ -exchanging ATPase) 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. PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. PPIs will only inhibit proton pumps that are actively secreting acid.<sup>1</sup> Following a meal approximately 70 to 80% of the proton pumps will be active.<sup>2</sup> Thus 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.<sup>1-3</sup>

Currently, there are six PPIs available on the market in a variety of formulations, including over-the-counter products. The PPIs include dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole; of which lansoprazole, omeprazole and pantoprazole are available generically. All PPIs are substituted benzimidazole derivatives and are structurally related. Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole represents a formulation that contains only the *S*-isomers of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer. Primary differences between the PPIs occur in their pharmacokinetic and pharmacodynamic properties along with formulation availability. Numerous studies have compared the various PPIs to one another. While some differences have been reported, the magnitude of these differences has been small and of questionable clinical significance.<sup>3</sup> In general, when given in equivalent dosages the PPIs have shown comparable efficacy.

The newest agent in the class, dexlansoprazole (Dexilant<sup>®</sup>), 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 used to be known by the brand name Kapidex<sup>®</sup> but has since been changed to Dexilant<sup>®</sup>.<sup>4</sup> Dexlansoprazole, the enantiomer of lansoprazole, is the first PPI with a Dual Delayed Release<sup>®</sup> 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.

Clinical studies have demonstrated that PPIs are effective for treatment of all acid-related disorders.<sup>3</sup> National and international consensus guidelines recognize PPIs as first-line therapy for the management of dyspepsia, GERD, peptic ulcer disease and eradication of *Helicobacter pylori*.<sup>19-24</sup> In addition, these agents have a role in the management of Barrett's Esophagus.<sup>25</sup> None of the current guidelines give preference to one PPI over another.

## Medications

**Table 1. Medications Included Within Class Review**

Generic Name (Trade name)	Medication Class	Generic Availability
Dexlansoprazole (Dexilent <sup>®</sup> )	Proton-pump inhibitors, single entity agents	-
Esomeprazole magnesium (Nexium <sup>®</sup> )	Proton-pump inhibitors, single entity agents	-
Esomeprazole sodium (Nexium IV <sup>®</sup> )	Proton-pump inhibitors, single entity agents	-
Lansoprazole (Prevacid <sup>®*</sup> , Prevacid SoluTab <sup>®*</sup> , Prevacid <sup>®</sup> 24HR)	Proton-pump inhibitors, single entity agents	✓
Omeprazole (Prilosec <sup>®*</sup> )	Proton-pump inhibitors, single entity agents	✓
Omeprazole magnesium (Prilosec <sup>®*</sup> , Prilosec OTC <sup>®*</sup> )	Proton-pump inhibitors, single entity agents	✓
Omeprazole with sodium bicarbonate (Zegerid <sup>®</sup> , Zegerid OTC <sup>®</sup> )	Proton-pump inhibitors, single entity agents	-
Pantoprazole (Protonix <sup>®*</sup> , Protonix IV <sup>®</sup> )	Proton-pump inhibitors, single entity agents	✓
Rabeprazole (Aciphex <sup>®</sup> )	Proton-pump inhibitors, single entity agents	-

\*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 treatment. In some cases a different dosage and/or length of therapy may be indicated for the maintenance treatment of a particular acid-related disorder.

**Table 2. Food and Drug Administration Approved Indications<sup>5-18</sup>**

Indication	Dexlansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
<b>Gastroesophageal Reflux Disease</b>						
Treatment of erosive esophagitis	✓	✓	✓	✓	✓	✓
Maintenance of healing of erosive esophagitis	✓	✓*	✓	✓	✓	✓
Treatment of symptomatic gastroesophageal reflux disease	✓	✓*	✓	✓	✓†	✓
<b>Peptic Ulcer Disease</b>						
<i>Helicobacter pylori</i> eradication to reduce the risk of duodenal ulcer recurrence		✓*‡	✓‡	✓ (Prilosec <sup>®</sup> )		✓‡
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 anti-inflammatory drug-		✓*	✓			

Indication	Dexlansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
associated gastric ulcer						
<b>Other</b>						
Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome		✓ *	✓	✓ (Prilosec®)	✓	✓
Risk reduction of upper gastrointestinal bleeding in critically ill patients				✓ (Zegerid®§)		
Treatment of frequent heartburn for up to 14 days			✓ (Prevacid® 24HR)	✓ (Prilosec 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.

### Pharmacokinetics

As noted in Table 3, there are some differences in the pharmacokinetic properties of the proton-pump inhibitors (PPIs), particularly with regards 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.<sup>27</sup> Depending upon their CYP2C19 genotype, patients may be considered extensive, intermediate or poor metabolizers.

Approximately 67% of Caucasians are extensive metabolizers and about 5% are slow metabolizers.<sup>3</sup> A few studies have reported higher cure rates for gastroesophageal reflux disease and eradication of *Helicobacter pylori* in patients who were poor metabolizers.<sup>3,27</sup> Additional studies are needed before definitive conclusions can be made regarding the use of certain PPIs in specific patient populations.

**Table 3. Pharmacokinetics**<sup>3,5-18</sup>

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	89 to 90 (multiple doses)	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	>80	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	0.5	77	CYP2C19 (none)	0.5 to 1.0
Pantoprazole	77	2.5	71	CYP2C19, CYP3A4 (not reported)	1
Rabeprazole	~52	2 to 5	90	CYP2C19, CYP3A4	1 to 2

Generic Name	Bioavailability (%)	Time to Peak Concentration (hours)	Renal Excretion (%)	Hepatic Metabolism (active metabolites)	Serum Half-Life (hours)
				(not reported)	

### Clinical Trials

Clinical trials have 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.<sup>28-69</sup> There is an abundance of data comparing the efficacy and safety of the individual PPIs for the treatment and/or management of these disorders. 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.<sup>28-30,48,51-53</sup> Richter et al reported that lansoprazole produced statistically quicker and greater symptomatic relief of GERD than omeprazole; however, the absolute differences in this trial were small and the clinical impact of the difference was not measured within the trial.<sup>49</sup>

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 at four and eight weeks.<sup>28,30,32,34,38,40,43,44</sup> Subgroup analyses in a few trials noted better healing rates with esomeprazole in patients with more severe disease.<sup>41,43</sup> Close analyses of all of these studies show that the overall differences were generally small. Though the results are statistically significant, the clinical significance of these differences is not clear. In addition, the results of these trials have not been replicated consistently in other trials, particularly in trials with lansoprazole and pantoprazole.<sup>31,33,39,42,45,47</sup> It should be noted that most trials comparing esomeprazole to omeprazole utilized a dose of 40 mg for esomeprazole and 20 mg for omeprazole.<sup>28,30,38,40</sup> 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.<sup>28</sup> Lightdale et al reported comparable healing rates and symptom relief in patients with erosive esophagitis treated with 20 mg/day of esomeprazole or omeprazole.<sup>42</sup> 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.<sup>58</sup>

Dexlansoprazole, the delayed-release formulation of the R-enantiomer of lansoprazole, was recently approved by the Food and Drug Administration, therefore direct comparison with the other agents is limited. 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 non-inferior 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.<sup>54</sup>

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) vs placebo (14.3%;  $P < 0.00001$  for both group comparisons) based upon crude rate analyses.<sup>55</sup> 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 ( $P < 0.00001$ ). Additionally, 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;  $P < 0.0025$ ).<sup>56</sup>

In a trial evaluating the efficacy and safety of dexlansoprazole 30 and 60 mg once daily vs 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 (54.9%, 50.5% and 18.5%, respectively;  $P < 0.00001$ ). There was no difference observed between the two active treatment groups. Additionally, 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.<sup>57</sup>

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.<sup>59-63,65-68</sup> One small trial reported higher eradication rates for patients treated with esomeprazole than pantoprazole.<sup>64</sup>

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.<sup>75</sup> 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.<sup>76</sup> 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.<sup>77</sup> 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
<b>Gastroesophageal Reflux Disease</b>				
<p>Klok et al<sup>28</sup></p> <p>Direct comparison of short-term PPI therapy under the same clinical conditions</p>	<p>MA</p> <p>RCTs of PPI use in GERD, PUD or <i>H pylori</i> eradication</p>	<p>41 trials</p> <p>Duration varied</p>	<p>Primary: Success rates (defined as endoscopically determined cure for GERD and PUD or absence of <i>H pylori</i>)</p> <p>Secondary: Not reported</p>	<p>Primary: Comparisons between PPI treatments for GERD included the following: esomeprazole 40 mg/day vs omeprazole 20 mg/day; esomeprazole 20 mg/day vs omeprazole 20 mg/day; lansoprazole 30 mg/day vs omeprazole 20 mg/day; lansoprazole 30 mg/day vs omeprazole 40 mg/day; lansoprazole 15 mg/day vs omeprazole 20 mg/day; lansoprazole 30 mg/day vs pantoprazole 40 mg/day; pantoprazole 40 mg/day vs omeprazole 20 mg/day; pantoprazole 20 mg/day vs omeprazole 20 mg/day; rabeprazole 20 mg/day vs omeprazole 20 mg/day and rabeprazole 10 mg/day vs omeprazole 20 mg/day.</p> <p>For GERD treatment, one statistically significant difference was noted. After four weeks of treatment, esomeprazole 40 mg/day was found to have significantly greater healing rates 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 found.</p> <p>Comparisons between PPI treatments for ulcer healing included the following: esomeprazole 40 mg/day vs omeprazole 20 mg/day; lansoprazole 30 mg/day vs omeprazole 20 mg/day; pantoprazole 40 mg/day vs omeprazole 20 mg/day; rabeprazole 20 mg/day vs omeprazole 20 mg/day.</p> <p>For PUD treatment, one statistically significant difference was noted. After four weeks of treatment, pantoprazole 40 mg/day was found to have significantly greater healing rates compared to omeprazole 20 mg/day (RR, 1.07; 95% CI, 1.02 to 1.13). For all other comparisons, no significant difference was found.</p> <p>No significant differences were found in <i>H pylori</i> eradication rates between PPIs.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Caro et al <sup>29</sup>  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 as follows: lansoprazole 30 mg/day, 6 to 29%; rabeprazole 20 mg/day, 9% and omeprazole 20 mg/day, 7 to 42%. No maintenance trials with pantoprazole were included.  Secondary: Not reported
Edwards et al <sup>30</sup>  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
Chey et al <sup>31</sup>  Esomeprazole 40 mg Daily  vs  lansoprazole 30 mg Daily	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 daytime and	Primary: No statistically significant differences were noted between the two treatment groups in symptom severity after day three ( <i>P</i> value not reported).  Secondary: No statistically significant differences were noted for any of the secondary endpoints ( <i>P</i> value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			nighttime heartburn after day one and symptom relief after day one and symptom severity after day one, seven and 14	
Castell et al <sup>32</sup>  Esomeprazole 40 mg Daily in the morning  vs  lansoprazole 30 mg Daily 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%; $P\leq 0.05$ ).  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 (7 vs 8 days; $P\leq 0.01$ ).  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%; $P\leq 0.05$ ).
Howden et al <sup>33</sup>  Esomeprazole 40 mg Daily  vs  lansoprazole 30 mg Daily	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 patients reporting	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 reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			heartburn-free days and nights, and rate of healing or improvement of esophagitis by two grades	<p>The percentage of patients reporting heartburn-free days and nights was comparable between treatment groups.</p> <p>Healing or improvement of esophagitis by two grades was observed in 90.0% of patients taking lansoprazole and 81.0% taking esomeprazole.</p>
<p>Devault et al<sup>34</sup></p> <p>Esomeprazole 20 mg Daily</p> <p>vs</p> <p>lansoprazole 15 mg Daily</p>	<p>DB, MC, PG, RCT</p> <p>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</p>	<p>N=1,026</p> <p>6 months</p>	<p>Primary: Remission rates (defined as no detectable erosive esophagitis and no study discontinuation due to reflux symptoms) estimated by Kaplan-Meier at six months</p> <p>Secondary: Observed remission rate at three months and six months</p>	<p>Primary: Estimated endoscopic/symptomatic remission rate during a period of six months was significantly higher (<math>P=0.0007</math>) for patients on esomeprazole (84.8%) compared to lansoprazole (75.9%).</p> <p>Secondary: Observed endoscopic/symptomatic remission rates at three months (92.8% vs 86.8%; <math>P&lt;0.0001</math>) and six months (86.2% vs 77.6%; <math>P&lt;0.0001</math>) were significantly higher in the esomeprazole group compared with the lansoprazole group.</p> <p>There was no significant difference between esomeprazole and lansoprazole at six months with regards 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%).</p> <p>Both treatments were well tolerated.</p>
<p>Fennerty et al<sup>35</sup></p> <p>Esomeprazole 40 mg Daily</p> <p>vs</p> <p>lansoprazole 30 mg Daily</p>	<p>DB, MC, RCT</p> <p>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-</p>	<p>N=999</p> <p>8 weeks</p>	<p>Primary: Healing rates at week eight</p> <p>Secondary: Resolution of heartburn symptoms at week four</p>	<p>Primary: Healing rates at week eight were significantly greater in patients taking esomeprazole compared to lansoprazole (82.4% vs 77.5%; <math>P=0.007</math>).</p> <p>Secondary: Significantly more patients taking esomeprazole had resolution of heartburn symptoms at week four than lansoprazole (72.0% vs 63.6%; <math>P=0.005</math>).</p>

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			
Metropole Study <sup>36</sup>  Esomeprazole 20 mg Daily  vs  lansoprazole 15 mg Daily	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
COMMAND Study <sup>37</sup>  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
<p>on-demand therapy vs lansoprazole 15 mg Daily</p> <p>All patients received esomeprazole 20 mg Daily for 2 to 4 weeks for acute treatment of GERD, then proceeded into the maintenance phase and were randomized into the above treatment groups.</p>	<p>of age with &gt;6 month history of GERD without esophageal mucosal breaks and reported symptoms in &gt;4 out of the previous seven days; patients were excluded if they received &gt;10 days of PPI therapy in the previous 28 days, were on anticholinergics, cisapride, prostaglandin analogues, NSAIDs or salicylates</p>		<p>from maintenance phase due to unwillingness to continue</p> <p>Secondary: Time to discontinuation due to insufficient heartburn control, patient satisfaction and symptom assessment</p>	<p>compared to lansoprazole (<math>P=0.001</math>). At six months, significantly more patients on lansoprazole were unwilling to continue therapy compared to esomeprazole (13% vs 6%; <math>P=0.001</math>).</p> <p>Secondary: Of the patients that discontinued therapy, 4.8% taking lansoprazole and 2.9% taking esomeprazole reported heartburn as the reason for unwillingness to continue (<math>P</math> 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 (<math>P=0.0028</math>).</p> <p>Patient satisfaction was significantly higher with esomeprazole after one month of treatment (<math>P=0.02</math>). At three and six months, patient satisfaction was similar for both groups.</p> <p>The frequency of heartburn symptoms recorded at clinic visits was higher with esomeprazole compared to lansoprazole at one, three and six months (<math>P</math> value not reported).</p>
<p>Richter et al<sup>38</sup></p> <p>Esomeprazole 40 mg Daily vs omeprazole 20 mg Daily</p>	<p>DB, MC, PG, RCT</p> <p>Adult patients with erosive esophagitis; patients were excluded if they tested positive for <i>H pylori</i>, had gastrointestinal bleeding, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal motility disorders, esophageal stricture, Barrett's esophagitis, duodenal or gastric ulcer,</p>	<p>N=2,425</p> <p>8 weeks</p>	<p>Primary: Healing rates at eight weeks</p> <p>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</p>	<p>Primary: Significantly more patients taking esomeprazole were healed at eight weeks compared to those taking omeprazole (93.7% vs 84.2%; <math>P&lt;0.001</math>).</p> <p>Secondary: Significantly more patients taking esomeprazole were healed at four weeks compared to those taking omeprazole (81.7% vs 68.7%; <math>P&lt;0.001</math>).</p> <p>Significantly more patients taking esomeprazole had complete resolution of heartburn compared to those taking omeprazole (68.3% vs 58.1%; <math>P&lt;0.001</math>). Time to first resolution was significantly greater with esomeprazole at day one (45.3% vs 32.0%; <math>P\leq 0.0005</math>) and day seven (85.6% vs 81.6%; <math>P\leq 0.0005</math>) compared to omeprazole.</p> <p>Time to sustained resolution with esomeprazole was significantly greater at day one, 14, and 28 compared to omeprazole (<math>P\leq 0.0005</math>).</p>

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 $P < 0.001$ ).
<p>Armstrong et al<sup>39</sup></p> <p>Esomeprazole 40 mg Daily</p> <p>vs</p> <p>esomeprazole 20 mg Daily</p> <p>vs</p> <p>omeprazole 20 mg Daily</p> <p>In study A, patients received either esomeprazole 40 mg Daily, esomeprazole 20 mg Daily, or omeprazole 20 mg Daily.</p> <p>In study B patients received esomeprazole 40 mg Daily or omeprazole 20 mg Daily.</p> <p>In study C, patients</p>	<p>3 DB, MC, PG, RCTs</p> <p>Patients with heartburn for &gt;6 months with a normal endoscopy were included in one of three trials</p>	<p>N=2,645</p> <p>4 weeks</p>	<p>Primary: Complete resolution of heartburn at four weeks</p> <p>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)</p>	<p>Primary: Complete resolution of heartburn at four weeks was comparable for all treatment arms throughout the three studies.</p> <p>Secondary: Complete resolution of heartburn at two weeks was comparable for all treatment arms throughout the three studies.</p> <p>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 (<math>P</math> value not reported).</p> <p>In study B, 73.5% taking esomeprazole 40 mg and 72.8% on omeprazole 20 mg reported adequate heartburn control (<math>P</math> value not reported).</p> <p>In study C, 67.9% taking esomeprazole 20 mg and 65.3% on omeprazole 20 mg reported adequate heartburn control (<math>P</math> value not reported).</p> <p>After four weeks, relief of other reflux and gastrointestinal symptoms was comparable in all treatment arms throughout the three studies.</p> <p>In study A, relief of heartburn reported by patients was higher with esomeprazole 20 mg (<math>P</math> value not reported). No differences were detected throughout the other two studies.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
received esomeprazole 20 mg Daily or omeprazole 20 mg Daily.				
Kahrilas et al <sup>40</sup>  Esomeprazole 40 mg Daily  vs  esomeprazole 20 mg Daily  vs  omeprazole 20 mg Daily	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%; $P<0.001$ vs omeprazole) and 20 mg (89.9%; $P<0.05$ vs 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 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 <sup>41</sup>  Esomeprazole 40 mg	DB, MC, PG, RCT  Patients 18 to 75 years	N=1,148  8 weeks	Primary: Proportion of patients with	Primary: The proportion of patients with healed erosive esophagitis at week eight was 92.2% for esomeprazole and 89.9% for omeprazole ( $P=0.189$ ).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Daily vs omeprazole 20 mg Daily	old with erosive esophagitis confirmed by endoscopy; patients were excluded if positive for <i>H pylori</i> , any bleeding disorder, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal strictures or Barrett's esophagus		healed erosive esophagitis at week eight  Secondary: Diary and investigator assessments of heartburn symptoms and safety	The proportion of patients with healed erosive esophagitis at week four was 71.5% for esomeprazole and 68.6% for omeprazole (no <i>P</i> value reported).  Healing rates with esomeprazole were significantly higher than those with omeprazole at weeks eight (88.4% vs 77.5%; <i>P</i> =0.007) and four (60.8% vs 47.9%; <i>P</i> =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%; <i>P</i> =0.48), the percentage of heartburn-free days (74.5% vs 73.0%; <i>P</i> =0.39) or the percentage of heartburn-free nights (86.2% vs 84.5%; <i>P</i> =0.21).  Both treatments had similar tolerability.
Lightdale et al <sup>42</sup>  Esomeprazole 20 mg Daily vs omeprazole 20 mg Daily	DB, MC, PG, RCT  Patients 18 to 75 years old with erosive esophagitis confirmed by endoscopy; patients excluded if positive for <i>H pylori</i> , 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 ( <i>P</i> =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 severity of erosive esophagitis.  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.
EXPO Study <sup>43</sup> (Treatment)  Esomeprazole 40 mg	DB, MC, RCT  Adult patients with erosive esophagitis	N=3,170  8 weeks	Primary: Healing rates at eight weeks	Primary: At eight weeks, healing rates for esomeprazole (95.5%) were statistically higher than for pantoprazole (92.0%; <i>P</i> <0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Daily vs pantoprazole 40 mg Daily	confirmed by endoscopy; patients were excluded if they had peptic ulcers, Zollinger-Ellison syndrome, esophageal stricture or Barrett's esophagitis		Secondary: Healing rates at four and eight weeks by baseline esophagitis severity, time to sustained symptom relief and proportion of heartburn-free days	Secondary: At four and eight weeks, healing rates for esomeprazole were statistically higher than for pantoprazole for erosive esophagitis grades B to D (Los Angeles grading; $P<0.05$ ). No significant difference was noted for grade A 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%; $P<0.01$ ).
EXPO Study <sup>44</sup> (Maintenance)  Esomeprazole 20 mg Daily  vs  pantoprazole 20 mg Daily	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%) than 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 <sup>45</sup>  Esomeprazole 40 mg Daily  vs  pantoprazole 40 mg Daily	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	N=217  4 weeks	Primary: Relief of GERD-related symptoms  Secondary: Relief rates of GERD-related symptoms, gastrointestinal	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	syndrome, pyloric stenosis and esophageal and/or gastrointestinal surgery		system rating scale score and time to first symptom relief	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 ( $P=0.034$ ).
Glatzel et al <sup>46</sup>  Esomeprazole 40 mg Daily for 4 weeks  vs  pantoprazole 40 mg Daily for 4 weeks	DB, MC, PG, RCT  Patients $\geq 18$ 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 <sup>®</sup> ), number of symptom episodes and rate of relapse  Secondary: Safety	Primary: Pantoprazole was shown to be as effective as esomeprazole based on mean ReQuest <sup>®</sup> 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 treatment groups.
EMANCIPATE Study <sup>47</sup>  Esomeprazole 20 mg Daily  vs  pantoprazole 20 mg Daily	DB, MC, PG, RCT  Patients $\geq 18$ years of age with endoscopically confirmed GERD who received four to eight weeks of pantoprazole 40 mg Daily and were healed; patients were excluded if they had Zollinger-Ellison	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
	syndrome or other gastric hypersecretory condition, pyloric stenosis, acute peptic ulcer and ulcer complications, endoscopically negative symptomatic GERD, esophageal strictures, Barrett's esophagus or pregnant or nursing			
Sharma et al <sup>48</sup>  Lansoprazole 30 mg Daily  vs  omeprazole 20 mg Daily	MA  DB RCT trials in patients with endoscopically diagnosed erosive esophagitis where healing rates had to be reported after four and/or eight weeks	N=2,040 (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 <sup>49</sup>  Lansoprazole 30 mg	DB, MC, RCT  Adult patients with	N=3,510  8 weeks	Primary: Percentage of heartburn-free	Primary: The percentage of heartburn-free days 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
Daily vs omeprazole 20 mg Daily	endoscopically documented erosive esophagitis; patients were excluded if they had gastrointestinal bleeding, history of gastric or esophageal surgery, esophageal motility disorders, esophageal stricture, or duodenal or gastric ulcers		days and nights following one to three days and one week of treatment and the frequency and severity of day- and nighttime heartburn  Secondary: Not reported	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 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 <sup>50</sup>  Lansoprazole 30 mg Daily  vs  omeprazole 20 mg Daily  vs  pantoprazole 40 mg Daily  vs  rabeprazole 20 mg Daily	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 vs lansoprazole (75.0%; $P<0.05$ ) in decreasing acid regurgitation.  Omeprazole (95.0%), pantoprazole (95.2%) and rabeprazole (100%) were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients who were <i>H pylori</i> positive were treated with the PPI and 2 antibiotics (amoxicillin, clarithromycin or metronidazole) for 7 days.				<p>more effective vs lansoprazole (82.6%; <math>P &lt; 0.05</math>) in decreasing epigastric pain.</p> <p>All four PPIs were well tolerated and there was no significant difference in the prevalence of adverse events among the four treatment groups.</p> <p>Secondary: Not reported</p>
Bardhan et al <sup>51</sup>  Omeprazole 20 mg Daily  vs  pantoprazole 20 mg Daily	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	<p>Primary: At two and four weeks, the rate of symptom relief was similar for pantoprazole (70% and 77%) and omeprazole (79% and 84%; <math>P</math> value not reported).</p> <p>Healing rates at four weeks were comparable between pantoprazole (84%) and omeprazole (89%; <math>P</math> value not reported).</p> <p>Healing rates at eight weeks were comparable between pantoprazole (90%) and omeprazole (95%; <math>P</math> value not reported).</p> <p>Secondary: Not reported</p>
Delcher et al <sup>52</sup>  Omeprazole 20 mg Daily  vs  rabeprazole 20 mg Daily  vs	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	<p>Primary: At four weeks, the rates of healing were comparable among rabeprazole Daily (94%), rabeprazole BID (93%) and omeprazole (98%; <math>P</math> value not reported).</p> <p>At four weeks, the rates of healing were comparable among rabeprazole Daily (97%), rabeprazole BID (98%) and omeprazole (100%; <math>P</math> value not reported).</p> <p>Secondary: At four and eight weeks, improvements in gastrointestinal symptoms were comparable among all treatment groups (<math>P</math> value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
rabeprazole 10 mg BID			physical well-being	Use of antacid tablets was comparable between all treatment groups ( <i>P</i> value not reported).  There were no significant differences between treatment groups in the General Well-Being Schedule (a quality-of-life measurement) or in a rating of overall physical well being.
Pace et al <sup>53</sup>  Omeprazole 20 mg Daily  vs  rabeprazole 20 mg Daily	DB, RCT  Patients with grade I to III GERD	N=560  8 weeks	Primary: Healing rates  Secondary: Time to first day with satisfactory relief	Primary: After eight weeks, rates of healing for rabeprazole (97.9%) were equivalent to omeprazole (97.5%).  Secondary: Rabeprazole had a statistically faster time to satisfactory relief (2.8 days) compared to omeprazole (4.7 days; <i>P</i> =0.0045).
Sharma et al <sup>54</sup>  Dexlansoprazole 60 mg Daily  vs  dexlansoprazole 90 mg Daily  vs  lansoprazole 30 mg Daily  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	Primary: Dexlansoprazole therapy was determined to be non-inferior 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 ( <i>P</i> <0.05).  Secondary: Complete healing of erosive esophagitis at week four was >64% in all treatment groups ( <i>P</i> 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 ( <i>P</i> <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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			severity, percentage days without rescue medication and adverse events	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.
<p>Howden et al<sup>55</sup></p> <p>Dexlansoprazole 60 mg Daily</p> <p>vs</p> <p>dexlansoprazole 90 mg Daily</p> <p>vs</p> <p>placebo</p> <p>Antacid use was permitted as rescue medication.</p>	<p>DB, MC, RCT</p> <p>Patients aged ≥18 years who had participated in 1 of 2 erosive esophagitis healing trials (see Sharma et al<sup>53</sup>) and had endoscopically proven healed erosive esophagitis</p>	<p>N=451</p> <p>6 months</p>	<p>Primary:</p> <p>Maintenance of healed erosive esophagitis</p> <p>Secondary:</p> <p>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</p>	<p>Primary:</p> <p>The maintenance rates of healed erosive esophagitis were significantly higher with dexlansoprazole therapy (86.6% and 82.1% with 60 and 90 mg respectively) vs placebo (25.7%; <math>P&lt;0.00001</math>)</p> <p>Secondary:</p> <p>The median days without heartburn were 95.8% and 94.4% for 60 and 90 mg dexlansoprazole, respectively vs 19.2% with placebo (<math>P&lt;0.00001</math> vs placebo) and the median heartburn-free nights were 98.3%, 97.1% and 50.0%, respectively (<math>P&lt;0.00001</math> vs placebo). The mean heartburn severity scores were 0.03 with dexlansoprazole 60 mg, 0.04 with dexlansoprazole 90 mg and 1.00 with placebo (<math>P&lt;0.00001</math> vs placebo). Median days without rescue medication were 94.9%, 93.6% and 27.5% (<math>P&lt;0.00001</math> vs placebo).</p> <p>Diarrhea, flatulence, gastritis and abdominal pain were the most frequently reported adverse events noted with dexlansoprazole therapy.</p>
<p>Metz et al<sup>56</sup></p> <p>Dexlansoprazole 30 mg Daily</p> <p>vs</p> <p>dexlansoprazole 60 mg Daily</p> <p>vs</p>	<p>DB, MC, RCT</p> <p>Patients aged ≥18 years who had participated in 1 of 2 erosive esophagitis healing trials (see Sharma et al<sup>53</sup>) and had endoscopically proven healed erosive esophagitis</p>	<p>N=445</p> <p>6 months</p>	<p>Primary:</p> <p>Maintenance of healed erosive esophagitis</p> <p>Secondary:</p> <p>Percentage of days and nights without heartburn, heartburn and GERD symptom severity (scale of</p>	<p>Primary:</p> <p>After six months, healing was maintained in 66.4%, 66.4% and 27.2% of dexlansoprazole 30 mg, 60 mg and placebo patients, respectively (<math>P&lt;0.00001</math>).</p> <p>Secondary:</p> <p>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; <math>P&lt;0.0025</math>). Also, 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</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo  Antacid use was permitted as rescue medication.			0=none to 4=very severe), percentage of days without rescue medication and adverse events	group reportedly heartburn free at night ( $P<0.0025$ ). Additionally, severity of symptoms was significantly lower with dexlansoprazole therapy (data not reported). Ninety-eight percent, 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 <sup>57</sup>  Dexlansoprazole 30 mg Daily  vs  dexlansoprazole 60 mg Daily  vs  placebo  Antacid use was permitted as rescue medication.	DB, MC, RCT  Patients aged $\geq 18$ 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 events	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 vs 18.5% with placebo ( $P<0.00001$ ).  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 active treatment vs placebo). The mean severity score of daytime/nighttime heartburn was 0.66, 0.69 and 1.04, respectively ( $P<0.00001$ for active treatment vs placebo). The median percentage of days without rescue medication was 63.0% for both dose of dexlansoprazole vs 37.3% with placebo ( $P<0.00001$ ).  The most frequently reported adverse events included diarrhea, headache and nausea and vomiting.
<b>Peptic Ulcer Disease</b>				
Choi et al <sup>59</sup>  Esomeprazole 40 mg BID  vs  omeprazole 20 mg BID	PRO, RCT  Patients who underwent upper endoscopy for various gastrointestinal symptoms with <i>H pylori</i> infection documented by histologic	N=576  1 week	Primary: <i>H pylori</i> eradication rates and side effects  Secondary: Not reported	Primary: In the ITT analysis, no difference was found between the eradication rates for esomeprazole (70.3%), omeprazole (64.9%), pantoprazole (69.3%) and rabeprazole (69.3%; $P=0.517$ ).  When eradication rates were analyzed according to whether patients had an ulcer or not on a per-protocol basis, no 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs pantoprazole 40 mg BID vs rabeprazole 20 mg BID PPI therapy was administered for 1 week along with amoxicillin 1 g BID and clarithromycin 500 mg BID.	examinations			pantoprazole and 82.8% for rabeprazole ( $P=0.833$ ). Eradication rates for patients with nonulcer dyspepsia were 87.5% for esomeprazole, 81.4% for omeprazole, 84.6% for pantoprazole and 73.1% for rabeprazole ( $P=0.412$ ). Side effects 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 <sup>60</sup> <i>H pylori</i> triple therapy with esomeprazole, lansoprazole, omeprazole, pantoprazole or rabeprazole	MA Randomized trials investigating <i>H pylori</i> 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 <sup>61</sup> <i>H pylori</i> triple therapy with lansoprazole, omeprazole, or pantoprazole with two	MA Clinical trials using PPI-based triple therapy for seven days in <i>H pylori</i> infections	N=8,383 (79 trials) 7 days	Primary: <i>H pylori</i> 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 <i>H pylori</i> eradication.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
other antibiotics for 7 days				Secondary: Not reported
Gisbert et al <sup>62</sup>  Esomeprazole-based <i>H pylori</i> therapies  vs  omeprazole-based <i>H pylori</i> therapies	MA  RCTs investigating the use of esomeprazole-based <i>H pylori</i> therapies and other PPI-based <i>H pylori</i> therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	Number of trials analyzed not reported  Treatment duration not reported	Primary: <i>H pylori</i> eradication rates for esomeprazole therapies  Secondary: Comparison of eradication rates for esomeprazole vs 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 <sup>63</sup>  Esomeprazole-based <i>H pylori</i> therapies  vs  omeprazole- and pantoprazole-based <i>H pylori</i> therapies	MA  RCTs investigating the use of esomeprazole-based <i>H pylori</i> therapies and other PPI-based <i>H pylori</i> therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	N=2,159 (11 trials)  1 week ( <i>H pylori</i> eradication)	Primary: <i>H pylori</i> eradication rates  Secondary: Not reported	Primary: The mean <i>H pylori</i> 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 significant differences.  No serious adverse events were reported.  Secondary: Not reported
Hsu et al <sup>64</sup>  Esomeprazole 40 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for 1 week  vs	PRO, RCT  Patients ≥18 years old, infected with <i>H pylori</i> , with endoscopically proven PUD or gastritis	N=200  8 weeks (follow-up endoscopy)	Primary: <i>H pylori</i> eradication rates, adverse events and compliance  Secondary: Ulcer healing	Primary: ITT analysis demonstrated a significantly higher eradication rate for patients in the esomeprazole group than for the pantoprazole group (94% vs 82%; <i>P</i> =0.009).  Both groups had similar frequencies of adverse events (15% vs 24%) and drug compliance (97% vs 96%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pantoprazole 40 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for 1 week				Secondary: Patients who had peptic ulcers diagnosed by initial endoscopy showed similar ulcer healing rates with esomeprazole (36/40) and pantoprazole (38/42) therapy.
Wu et al <sup>65</sup>  Esomeprazole 40 mg Daily, amoxicillin 1 g BID and clarithromycin 500 mg BID for 1 week  vs  rabeprazole 20 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for 1 week	PRO, RCT  Patients with gastritis or peptic ulcer with <i>H pylori</i> infection	N=420  12 to 16 weeks (follow-up)	Primary: <i>H pylori</i> eradication rates, adverse events and compliance  Secondary: Not reported	Primary: ITT analysis revealed that the eradication rate was 89.4% in the esomeprazole group and 90.5% in the rabeprazole group ( $P=0.72$ ).  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 <sup>66</sup>  Lansoprazole-based <i>H pylori</i> therapies  vs  omeprazole-based <i>H pylori</i> therapies	MA  RCTs investigating the use of lansoprazole-based <i>H pylori</i> therapies and other PPI-based <i>H pylori</i> therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	N=1,354  16 trials	Primary: <i>H pylori</i> 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).  Mean eradication rates for triple therapy with lansoprazole were significantly higher than observed with 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 <sup>67</sup>  Pantoprazole-based <i>H pylori</i> therapies	MA  RCTs investigating the use of pantoprazole-	12 trials  Treatment duration not	Primary: <i>H pylori</i> eradication rates for pantoprazole	Primary: Fourteen-day therapy with pantoprazole 40 mg BID and clarithromycin 500 mg TID therapy resulted in a mean eradication rate of 60%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs  lansoprazole- or omeprazole-based <i>H pylori</i> therapies	based <i>H pylori</i> therapies and lansoprazole- or omeprazole-based <i>H pylori</i> therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	reported	therapies  Secondary: Comparison of eradication rates for pantoprazole vs other similar (same antibiotics and duration of use) PPI therapies, comparison of pantoprazole therapies to similar omeprazole and lansoprazole therapies	Mean eradication rates following seven day therapies were as follows: pantoprazole-amoxicillin-clarithromycin 78%, pantoprazole-clarithromycin-nitroimidazole 84% and pantoprazole-amoxicillin-nitroimidazole 74%.  Secondary: Mean eradication rates for pantoprazole-based therapies (83%) with antibiotics were comparable to other PPI-based therapies (81%; OR, 1.00; 95% CI, 0.61 to 1.64).  Mean eradication rates for pantoprazole-based therapies (83%) were comparable to omeprazole-based therapies (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).
Gisbert et al <sup>68</sup>  Rabeprazole-based <i>H pylori</i> therapies  vs  lansoprazole- or omeprazole-based <i>H pylori</i> therapies	MA  RCTs investigating the use of rabeprazole-based <i>H pylori</i> therapies and lansoprazole- or omeprazole-based <i>H pylori</i> therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	12 trials  Treatment duration not reported	Primary: <i>H pylori</i> eradication rates for rabeprazole therapies  Secondary: Comparison of eradication rates for rabeprazole vs other similar (same antibiotics and duration of use) PPI therapies, comparison of rabeprazole therapies to	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			similar omeprazole and lansoprazole therapies	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).
<b>Other</b>				
<p>Ramdani et al<sup>69</sup></p> <p>Lansoprazole 30 to 120 mg/day or omeprazole 20 to 100 mg/day</p> <p>vs</p> <p>pantoprazole 40 to 200 mg/day</p> <p>If previously maintained on lansoprazole or omeprazole received pantoprazole for 7 to 10 days.</p>	<p>OL, PRO</p> <p>Adult patients with Zollinger-Ellison 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</p>	<p>N=11</p> <p>7-10 days</p>	<p>Primary: Median 24-hour intragastric pH and percentage of time at or below pH 3, 4, 5 and 6</p> <p>Secondary: Basal acid output</p>	<p>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; <math>P=0.90</math>).</p> <p>There were no significant differences in percentage of time at or below pH 3, 4, 5 and 6 between pantoprazole and lansoprazole or omeprazole (<math>P&gt;0.05</math>).</p> <p>Secondary: Median basal acid output was similar between pantoprazole and lansoprazole or omeprazole (<math>P</math> value not reported).</p>
<p>Conrad et al<sup>70</sup></p> <p>Omeprazole IR suspension (two 40 mg dose on day 1 then 40 mg/day thereafter)</p> <p>vs</p> <p>cimetidine intravenous (300 mg bolus then 50 mg/hour thereafter)</p>	<p>DB, RCT</p> <p>Hospitalized patients &gt;16 years old in the intensive care unit with an anticipated stay <math>\geq 72</math> hours with &gt;1 additional risk for upper gastrointestinal bleed; patients were excluded for history of gastric surgery, allergy to cimetidine or omeprazole, active</p>	<p>N=359</p> <p>14 days</p>	<p>Primary: Clinically significant upper gastrointestinal bleed</p> <p>Secondary: Median gastric pH on each trial day, percentage of patients with median gastric pH of &gt;4 on each trial day and the</p>	<p>Primary: Clinically significant upper gastrointestinal bleeding was observed in seven (3.9%) patients taking omeprazole compared to ten (5.5%) patients taking cimetidine (<math>P</math> 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 "noninferiority" margin.</p> <p>Secondary: Median gastric pH was significantly higher in patients taking omeprazole compared to cimetidine (median pH values not reported; <math>P&lt;0.001</math>).</p> <p>A significantly higher percentage of patients on omeprazole had median daily gastric pH &gt;4 compared to patients on cimetidine (<math>P\leq 0.01</math> on days one to 13, <math>P=0.2</math> on day 14).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	gastrointestinal bleeding, significant risk of swallowing blood, enteral feeding required for the first two 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		percentage of patients with inadequate gastric pH control (two consecutive pH measurements of $\leq 4$ )	A significantly higher percentage of patients on cimetidine had inadequate gastric pH control (58%) compared to omeprazole (18.0%; $P < 0.001$ ).
<p>Katz et al<sup>71</sup></p> <p>Omeprazole IR suspension 40 mg for 7 days</p> <p>vs</p> <p>esomeprazole 40 mg for 7 days</p> <p>vs</p> <p>lansoprazole 30 mg for 7 days</p> <p>Following a 10 to 14 day washout between treatment periods, patients were XO to one of the alternative</p>	<p>OL, RCT, XO</p> <p>Non-Asian patients <math>\geq 18</math> 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 <math>\leq 2.5</math> prior to randomization; patients were excluded for concurrent gastrointestinal diseases other than GERD, a significant history of gastrointestinal</p>	<p>N=54</p> <p>Each treatment was for 7 days</p>	<p>Primary:</p> <p>Occurrence of nocturnal acid breakthrough (gastric pH <math>&lt; 4</math> for more than one hour during the night-time from 22:00 to 06:00 hours)</p> <p>Secondary:</p> <p>Percentage of time gastric pH <math>&gt; 4</math> and median gastric pH in cumulative two-hour increments during the nighttime period and over 24 hours</p>	<p>Primary:</p> <p>After seven days of Daily bedtime dosing, omeprazole significantly reduced nocturnal acid breakthrough compared with esomeprazole and lansoprazole (61% vs 92% and 92%; <math>P &lt; 0.001</math> for both comparisons).</p> <p>Secondary:</p> <p>During the first half of the night, percentage of time with gastric pH <math>&gt; 4</math> 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; <math>P &lt; 0.001</math> for both comparisons).</p> <p>Over the eight hour nighttime period, percentage of time with gastric pH <math>&gt; 4</math> and median gastric pH were significantly higher after omeprazole (53% and 4.04, respectively) than lansoprazole (34% and 2.09, respectively; <math>P &lt; 0.001</math> for both comparisons) but comparable to esomeprazole (55% and 4.85, respectively).</p> <p>The percentage of time with gastric pH <math>&gt; 4</math> for the 24-hour period was 44% with omeprazole vs 59% with esomeprazole (<math>P &lt; 0.001</math>) and 28% with lansoprazole (<math>P &lt; 0.001</math> for both comparisons).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treatments.	diseases in the past five years and any history of gastric surgery or any other significant unstable illness			
<p>Castell et al<sup>72</sup></p> <p>Omeprazole IR suspension dosed 40 mg/day for 1 week, then 20 or 40 mg BID for 1 day</p> <p>vs</p> <p>pantoprazole 40 mg/day for 1 week, then 40 mg BID for 1 day</p> <p>Participants underwent 8 days of treatment followed by a 10 to 14 day washout period then an additional 8 days of treatment on the other agent.</p>	<p>OL, RCT, XO</p> <p>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</p>	<p>N=36</p> <p>16 days</p>	<p>Primary: Control of nocturnal gastric acidity measured by the following: percentage of time with gastric pH &gt;4, median gastric pH and nocturnal acid breakthrough</p> <p>Secondary: Not reported</p>	<p>Primary: Median percentage of time with gastric pH &gt;4 was significantly higher with omeprazole (54.7%) compared to pantoprazole (26.5%; <math>P&lt;0.001</math>).</p> <p>Median gastric pH was significantly higher with omeprazole (4.7) compared to pantoprazole (2.0; <math>P&lt;0.001</math>).</p> <p>Significantly less nocturnal acid breakthrough was observed with omeprazole (53.1%) compared to pantoprazole (78.1%; <math>P=0.005</math>).</p> <p>Secondary: Not reported</p>
<p>Regula et al<sup>73</sup></p> <p>Omeprazole 20 mg Daily</p> <p>vs</p> <p>pantoprazole 20 mg</p>	<p>DB, MC, PG, RCT</p> <p>Rheumatic patients &gt;55 years of age on continual NSAIDs and with at least one more recognized risk factor that contributes to the</p>	<p>N=595</p> <p>6 months</p>	<p>Primary: Therapeutic failure (peptic ulcer, &gt;10 erosions or petechiae in the stomach or duodenum, reflux esophagitis, or</p>	<p>Primary: After six months, the probabilities to remain in remission were 90% with pantoprazole 20 mg, 93% with pantoprazole 40 mg and 89% with omeprazole for lack of therapeutic failure (<math>P</math> values not reported).</p> <p>After six months, the probabilities to remain in remission were 91% with pantoprazole 20 mg, 95% with pantoprazole 40 mg and 93% with omeprazole for lack of endoscopic failure (<math>P</math> values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Daily vs pantoprazole 40 mg Daily	development of gastrointestinal injury; patients were excluded if they had Zollinger-Ellison syndrome, esophageal structures, previous surgery of the gastrointestinal tract, current peptic ulcer or peptic ulcer complication		discontinuation due to gastrointestinal symptoms or an adverse event) and lack of endoscopic failure at six months and adverse events  Secondary: Primary end points at three months	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; 33% of patients receiving omeprazole; <i>P</i> values not reported).  Secondary: After three months, the probabilities to remain in remission were 94% with pantoprazole 20 mg, 97% with pantoprazole 40 mg and 94% with omeprazole for lack of therapeutic failure ( <i>P</i> values not reported).  After three months, the probabilities to remain in remission were 96% with pantoprazole 20 mg, 99% with pantoprazole 40 mg and 96% with omeprazole for lack of endoscopic failure ( <i>P</i> values not reported).
Chan et al <sup>74</sup>  Diclofenac (slow release) 75 mg BID plus omeprazole 20 mg Daily  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 <i>H pylori</i> negative (patients 18 to 59 years of age were enrolled if they had a documented history of gastroduodenal	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	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; <i>P</i> <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; <i>P</i> value not reported).  Secondary: Least-squares mean change from baseline to visit six in Patients' Global Assessment of Arthritis showed an improvement of 0.75 (0.02) in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	ulceration or gastrointestinal hemorrhage $\geq$ 90 days before screening)		withdrawal due to gastrointestinal adverse events	<p>celecoxib group and 0.77 (0.02) in the diclofenac plus omeprazole group (<math>P=0.41</math>).</p> <p>Regarding clinically significant events throughout the gastrointestinal tract plus symptomatic ulcers (defined as ulcer on endoscopy in a patient with dyspepsia), fewer events were reported for patients who received celecoxib (n=25; 1%) than for patients who received diclofenac plus omeprazole (n=92; 5%; <math>P&lt;0.0001</math>).</p> <p>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 (<math>P=0.03</math>).</p> <p>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 (<math>P=0.0006</math>).</p>

Drug regimen abbreviations: BID=twice daily, IR=immediate-release, TID=three times daily

Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, TD=triple-dummy, XO=crossover

Miscellaneous abbreviations: GERD=gastroesophageal reflux disease, *H pylori*=*Helicobacter pylori*, NSAIDs=nonsteroidal anti-inflammatory drugs, PPI=proton-pump inhibitor, PUD=peptic ulcer disease

**Special Populations**

**Table 5. Special Populations**<sup>5-18</sup>

Generic Name	Population and Precaution					
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
Dexlansoprazole	No dosage adjustment required in the elderly.  Safety and efficacy in children have not been established.	No dosage adjustment required.	Hepatic dose adjustment should be considered in severe liver disease.	B	Unknown	N/A
Esomeprazole magnesium	No dosage adjustment required in the elderly.  FDA approved for use in children 1 to 17 years 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	N/A
Esomeprazole sodium	No dosage adjustment required in the elderly.  Safety and efficacy in children have not been established.	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	N/A

Generic Name	Population and Precaution					
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
Lansoprazole	No dosage adjustment required in the elderly.  FDA approved for use in children 1 to 17 years of age.	No dosage adjustment required.	Hepatic dose adjustment should be considered in severe liver disease.	B	Unknown	Orally disintegrating tablets contain phenylalanine.
Omeprazole	No dosage adjustment required in the elderly.  FDA approved for use in children 1 to 16 years of age.	No dosage adjustment required.	Hepatic dose adjustment should be considered for the maintenance of healing of erosive esophagitis.	C	Yes (% unknown)	Dose adjustment should be considered for Asian patients, particularly for the maintenance of healing of erosive esophagitis.
Omeprazole magnesium	No dosage adjustment required in the elderly.  FDA approved for use in children 1 to 16 years of age.	No dosage adjustment required.	Hepatic dose adjustment should be considered for the maintenance of healing of erosive esophagitis.	C	Yes (% unknown)	Dose adjustment should be considered for Asian patients, particularly for the maintenance of healing of erosive esophagitis.
Omeprazole with sodium bicarbonate	No dosage adjustment required in the elderly.  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 (% unknown)	Dose adjustment should be considered for Asian patients, particularly for the maintenance of healing of erosive esophagitis.  Caution is advised for patients on a

Generic Name	Population and Precaution					
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
						sodium-restricted diet.
Pantoprazole	No dosage adjustment required in the elderly.  FDA approved for the short-term treatment of erosive esophagitis associated with GERD in children ≥5 years of age.	No dosage adjustment required.	No dosage adjustment required.*	B	Unknown	N/A
Rabeprazole	No dosage adjustment required in the elderly.  FDA 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	N/A

FDA=Food and Drug Administration, GERD=gastroesophageal reflux disease, N/A=not applicable  
 \*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.<sup>78</sup> 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.<sup>20</sup> Additional studies are needed to determine the value of osteoprotective medications for patients receiving long-term therapy with PPIs.<sup>78</sup>

**Table 6. Adverse Drug Events (%)<sup>5-18</sup>**

Adverse Event(s)	Dexlansoprazole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansoprazole	Omeprazole	Omeprazole Magnesium	Omeprazole Sodium Bicarbonate	Pantoprazole	Rabeprazole
<b>Cardiac Disorders</b>									
Atrial fibrillation	-	-	-	-	-	-	6.2*	-	-
Bradycardia	-	-	-	-	-	-	3.9*	-	-
Supraventricular tachycardia	-	-	-	-	-	-	3.4*	-	-
Tachycardia	-	-	-	-	-	-	3.4*	-	-
Ventricular tachycardia	-	-	-	-	-	-	4.5*	-	-
<b>Central Nervous System</b>									
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	-	-	-	✓	-	-	-	-	-
Headache	-	1.9 to 8.1	10.9	✓	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	-	-	-	-	-	-	-
<b>Dermatological</b>									
Erythema multiforme	-	✓	-	-	-	-	-	-	-
Rash	-	-	-	-	1.5	1.5	1.5	≤2	-
Stevens-Johnson syndrome	-	✓	-	-	-	-	-	✓	✓
Toxic epidermal necrolysis	-	✓	-	-	-	-	-	✓	-
<b>Endocrine and Metabolic</b>									
Liver function abnormalities	-	-	-	-	-	-	1.7*	2	-
<b>Gastrointestinal</b>									
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	-	-	-	-	-	-	-	✓	-
Constipation	-	✓	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

Adverse Event(s)	Dexlansoprazole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansoprazole	Omeprazole	Omeprazole Magnesium	Omeprazole Sodium Bicarbonate	Pantoprazole	Rabeprazole
Dry mouth	-	✓	3.9	-	-	-	-	-	-
Dyspepsia	-	-	6.4	-	-	-	-	≥1	-
Flatulence	1.4 to 2.6	✓	10.3	-	2.7	2.7	2.7	2 to 4	3
Gastric hypomotility	-	-	-	-	-	-	1.7	-	-
Gastroenteritis	-	-	-	-	-	-	-	≥1	-
Hepatotoxicity	-	-	-	-	✓	✓	✓	-	-
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	-	✓	-	-	✓	✓	✓	-	-
Vomiting	1.4 to 2.2	-	-	-	1.5 to 3.2	1.5 to 3.2	1.5 to 3.2	2	3.6
<b>Genitourinary</b>									
Interstitial nephritis	-	-	-	-	✓	✓	✓	-	-
Urinary tract infection	-	-	-	-	-	-	2.2*	≥1	-
<b>Hematologic</b>									
Thrombocytopenia	-	-	-	-	-	-	10.1*	✓	-
<b>Infections and Infestations</b>									
Candidal infection	-	-	-	-	-	-	1.7*	-	-
Oral candidiasis	-	-	-	-	-	-	3.9*	-	-
Sepsis	-	-	-	-	-	-	5.1*	-	-
<b>Laboratory Test Abnormalities</b>									
Elevated serum glutamic pyruvic transaminase	-	-	-	-	-	-	-	≥1	-
<b>Metabolism and Nutrition Disorders</b>									
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*	-	-
<b>Musculoskeletal</b>									
Arthralgia	-	-	-	-	-	-	-	≥1	-
Back pain	-	-	-	-	1.1	1.1	1.1	≥1	-
Hip fracture	-	✓	-	✓	✓	✓	✓	✓	✓

Adverse Event(s)	Dexlansoprazole	Esomeprazole Magnesium	Esomeprazole Sodium	Lansoprazole	Omeprazole	Omeprazole Magnesium	Omeprazole Sodium Bicarbonate	Pantoprazole	Rabeprazole
Pain	-	-	-	-	-	-	-	-	3
Rhabdomyolysis	-	✓	-	✓	✓	✓	✓	✓	✓
<b>Respiratory</b>									
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	-
<b>Other</b>									
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	-	-	-	-	✓	✓	✓	-	-
Flu-like syndrome	-	-	-	-	-	-	-	≥1	-
Hyperpyrexia	-	-	-	-	-	-	4.5*	-	-
Hypertension	-	-	-	-	-	-	7.9*	-	-
Hypotension	-	-	-	-	-	-	9.6*	-	-
Infection	-	-	-	-	-	-	-	-	2
Oedema	-	-	-	-	-	-	1.7*	-	-
Pruritis	-	-	1.1	-	-	-	-	-	-
Pyrexia	-	-	-	-	-	-	20.2*	-	-
Rash	-	-	-	-	-	-	5.6*	-	-

✓ Percent not specified.

- Event not reported or incidence <1%.

\* Critically ill patients who were administered omeprazole sodium bicarbonate.

**Contraindications/Precautions**

Proton-pump inhibitors (PPIs) are contraindicated in patients with known hypersensitivity to substituted benzimidazoles.<sup>5-16</sup> Symptomatic response to PPIs does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in patients receiving long-term pantoprazole and omeprazole therapy. Generally, daily treatment with any acid-suppressing medication over a long period of time (e.g., longer than three years) may lead to malabsorption of cyanocobalamin (Vitamin B12).

Each Zegerid<sup>®</sup> (omeprazole with sodium bicarbonate) capsule contains 1,100 mg (13 mEq) of sodium bicarbonate.<sup>17</sup> The total content of sodium in each capsule is 304 mg. Each packet of Zegerid<sup>®</sup> powder for oral suspension contains 1,680 mg (20 mEq) of sodium bicarbonate (equivalent to 460 mg of Na<sup>+</sup>). The sodium content of Zegerid<sup>®</sup> products should be taken into consideration when administering to patients on a sodium-restricted diet. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

**Drug Interactions**

There has been some recent controversy surrounding the coadministration of proton-pump inhibitors (PPIs) with clopidogrel, particularly omeprazole. The Food and Drug Administration issued a warning in November of 2009 to avoid using omeprazole with clopidogrel due to the potential reduction of anti-platelet activity by approximately one half.<sup>79</sup> Table 7 includes additional significant drug interactions with the PPIs.

**Table 7. Drug Interactions<sup>5</sup>**

Generic Name	Interacting Medication or Disease	Potential Result
Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole	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.
Dexlansoprazole, esomeprazole, lansoprazole, 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. An H <sub>2</sub> receptor antagonist may be a safer alternative.
Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole	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.
Omeprazole	Cilostazol	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.

**Dosage and Administration**

To maximize efficacy, Proton-pump inhibitors (PPIs) should be taken before the first meal of the day.<sup>3</sup> 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.<sup>8,15,17</sup>

The dexlansoprazole and omeprazole delayed-release capsules can be administered orally; either swallowed whole or sprinkled on applesauce.<sup>13,18</sup> The esomeprazole magnesium and lansoprazole delayed-release capsules and the pantoprazole delayed-release suspension can be administered orally or through a nasogastric tube.<sup>9,11,15</sup> The omeprazole with sodium bicarbonate powder for oral suspension can be administered orally or through a nasogastric or orogastric tube.<sup>17</sup> The esomeprazole magnesium and omeprazole magnesium delayed-release suspension can be administered orally or through a nasogastric or gastric tube.<sup>9,13</sup> The lansoprazole delayed-release disintegrating tablets can be administered orally or through a nasogastric tube or with an oral syringe.<sup>11</sup>

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.<sup>17</sup> 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 8. Dosing and Administration**<sup>8-18</sup>

Generic Name	Adult Dose	Pediatric Dose	Availability
Dexlansoprazole	<p><u>Treatment of symptomatic GERD:</u> Delayed-release capsule: 30 mg Daily for 4 weeks</p> <p><u>Treatment of erosive esophagitis:</u> Delayed-release capsule: 60 mg Daily for up to 8 weeks</p> <p><u>Maintenance of healing of erosive esophagitis:</u> Delayed-release capsule: 30 mg Daily*</p>	Safety and efficacy in children have not been established.	Delayed-release capsule: 30 mg 60 mg
Esomeprazole magnesium	<p><u>Treatment of symptomatic GERD:</u> Delayed-release capsule, delayed-release solution: 20 mg Daily for 4 weeks<sup>†</sup></p> <p><u>H pylori eradication to reduce the risk of duodenal ulcer recurrence:</u> Delayed-release capsule, delayed-release suspension: 40 mg Daily for 10 days<sup>‡</sup></p> <p><u>Treatment of erosive esophagitis:</u> Delayed-release capsule, delayed-release solution: 20 or 40 mg Daily for 4 to 8 weeks<sup>§</sup></p> <p><u>Maintenance of healing of erosive esophagitis:</u> Delayed-release capsule, delayed-release solution: 20 mg Daily*</p> <p><u>Treatment of pathological</u></p>	<p><u>Treatment of symptomatic GERD in children 1 to 11 years of age:</u> Delayed-release capsule, delayed-release solution: 10 mg Daily for up to 8 weeks<sup>†</sup></p> <p><u>Treatment of symptomatic GERD in children 12 to 17 years of age:</u> Delayed-release capsule, delayed-release solution: 20 or 40 mg Daily for up to 8 weeks</p> <p><u>Treatment of erosive esophagitis in</u></p>	<p>Delayed-release capsule: 20 mg 40 mg</p> <p>Delayed-release suspension: 10 mg 20 mg 40 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p><u>hypersecretory conditions, including Zollinger-Ellison syndrome:</u> Delayed-release capsule, delayed-release suspension: 40 mg BID<sup>  </sup></p> <p><u>Risk reduction of NSAID associated gastric ulcer:</u> Delayed-release capsule, delayed-release suspension: 20 or 40 mg Daily for up to 6 months*</p>	<p><u>children 1 to 11 years:</u> Delayed-release capsule, delayed-release solution: 10 or 20 (<math>\geq 20</math> kg) mg Daily for 8 weeks<sup>  </sup></p>	
Esomeprazole sodium	<p><u>Treatment of symptomatic GERD<sup>#</sup>:</u> Solution for injection: 20 or 40 mg Daily</p>	<p>Safety and efficacy in children have not been established.</p>	<p>Solution for injection: 20 mg 40 mg</p>
Lansoprazole	<p><u>Treatment of symptomatic GERD:</u> Delayed-release capsule, delayed-release disintegrating tablet: 15 mg Daily for up to 8 weeks</p> <p><u>H pylori eradication to reduce the risk of duodenal ulcer recurrence:</u> Delayed-release capsule, delayed-release disintegrating tablet: 30 mg BID for 10 or 14 days<sup>†</sup> or 30 mg TID for 14 days**</p> <p><u>Treatment of active duodenal ulcers:</u> Delayed-release capsule, delayed-release disintegrating tablet: 15 mg Daily for 4 weeks</p> <p><u>Treatment of erosive esophagitis:</u> Delayed-release capsule, delayed-release disintegrating tablet: 30 mg Daily for up to 8 weeks<sup>††</sup></p> <p><u>Treatment of active, benign gastric ulcer:</u> Delayed-release capsule, delayed-release disintegrating tablet: 30 mg Daily up to 8 weeks</p> <p><u>Healing of NSAID associated gastric ulcer:</u> Delayed-release capsule, delayed-release disintegrating tablet: 30 mg Daily for 8 weeks<sup>††</sup></p> <p><u>Maintenance of healing duodenal ulcers:</u> Delayed-release capsule, delayed-release disintegrating tablet: 15 mg Daily</p>	<p><u>Treatment of symptomatic GERD in children 1 to 11 years of age:</u> Delayed-release capsule, delayed-release disintegrating tablet: 15 (<math>\leq 30</math> kg) or 30 (<math>&gt; 30</math> kg) mg Daily for up to 12 weeks<sup>  †</sup></p> <p><u>Treatment of symptomatic GERD in children 12 to 17 years old:</u> Delayed-release capsule, delayed-release disintegrating tablet: 30 mg Daily for up to 8 weeks</p> <p><u>Treatment of erosive esophagitis in children 1 to 11 years of age:</u> Delayed-release capsule, delayed-release disintegrating tablet: 15 (<math>\leq 30</math> kg) or 30 (<math>&gt; 30</math> kg) mg Daily for up to 12 weeks<sup>  †</sup></p> <p><u>Treatment of erosive esophagitis in children 12 to 17 years of age:</u> Delayed-release capsule, delayed-release disintegrating tablet: 30 mg Daily for up to 8 weeks</p>	<p>Delayed-release capsule: 15 mg 30 mg</p> <p>Delayed-release capsule (OTC): 15 mg</p> <p>Delayed-release disintegrating tablet: 15 mg 30 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p><u>Maintenance of healing of erosive esophagitis:</u> Delayed-release capsule, delayed-release disintegrating tablet: 15 mg Daily</p> <p><u>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome:</u> Delayed-release capsule, delayed-release disintegrating tablet: 60 mg Daily<sup>ss</sup></p> <p><u>Risk reduction of NSAID associated gastric ulcer:</u> Delayed-release capsule, delayed-release disintegrating tablet: 15 mg Daily up to 12 weeks<sup>tt</sup></p> <p><u>Treatment of frequent heartburn:</u> Delayed-release capsule (OTC): 15 mg Daily for 14 days<sup>ss</sup></p>		
Omeprazole	<p><u>Treatment of symptomatic GERD<sup>##</sup>:</u> Delayed-release capsule: 20 mg Daily for 4 weeks</p> <p><u><i>H pylori</i> eradication to reduce the risk of duodenal ulcer recurrence:</u> Delayed-release capsule: 20 mg BID for 10 days<sup>***</sup> or 40 mg Daily for 14 days<sup>ttt</sup></p> <p><u>Treatment of active duodenal ulcers:</u> Delayed-release capsule: 20 mg Daily for 4 weeks<sup>ttt</sup></p> <p><u>Treatment of erosive esophagitis<sup>sss</sup>:</u> Delayed-release capsule: 20 mg Daily for 4 to 8 weeks</p> <p><u>Treatment of active, benign gastric ulcer:</u> Delayed-release capsule: 40 mg Daily for 4 to 8 weeks</p> <p><u>Maintenance of healing of erosive esophagitis:</u> Delayed-release capsule: 20 mg Daily<sup>     </sup></p> <p><u>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome:</u> Delayed-release capsule: 60 mg</p>	<p><u>Treatment of symptomatic GERD in children 1 to 16 years of age:</u> Delayed-release capsule: 5 (5 to 10 kg), 10 (10 to 20 kg) or 20 (≥20 kg) mg Daily</p> <p><u>Maintenance of healing of erosive esophagitis in children 1 to 16 years of age:</u> Delayed-release capsule: 5 (5 to 10 kg), 10 (10 to 20 kg) or 20 (≥20 kg) mg Daily</p>	<p>Delayed-release capsule: 10 mg 20 mg 40 mg</p> <p>Delayed-release tablet (OTC): 20 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p>Daily<sup>    </sup></p> <p><u>Treatment of frequent heartburn:</u> Delayed-release tablet (OTC): 20 mg Daily for 14 days<sup>SS</sup></p>		
<p>Omeprazole magnesium</p>	<p><u>Treatment of symptomatic GERD<sup>##</sup>:</u> Delayed-release capsule: 20 mg Daily for 4 weeks</p> <p><u>H pylori eradication to reduce the risk of duodenal ulcer recurrence:</u> Delayed-release capsule: 20 mg BID for 10 days<sup>***</sup> or 40 mg Daily for 14 days<sup>+++</sup></p> <p><u>Treatment of active duodenal ulcers:</u> Delayed-release capsule: 20 mg Daily for 4 weeks<sup>+++</sup></p> <p><u>Treatment of erosive esophagitis<sup>SSS</sup>:</u> Delayed-release capsule: 20 mg Daily for 4 to 8 weeks</p> <p><u>Treatment of active, benign gastric ulcer:</u> Delayed-release capsule: 40 mg Daily for 4 to 8 weeks</p> <p><u>Maintenance of healing of erosive esophagitis:</u> Delayed-release capsule: 20 mg Daily<sup>    </sup></p> <p><u>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome:</u> Delayed-release capsule: 60 mg Daily<sup>    </sup></p> <p><u>Treatment of frequent heartburn:</u> Delayed-release tablet (OTC): 20 mg Daily for 14 days<sup>SS</sup></p>	<p><u>Treatment of symptomatic GERD in children 1 to 16 years of age:</u> Delayed-release capsule: 5 (5 to 10 kg), 10 (10 to 20 kg) or 20 (≥20 kg) mg Daily</p> <p><u>Maintenance of healing of erosive esophagitis in children 1 to 16 years of age:</u> Delayed-release capsule: 5 (5 to 10 kg), 10 (10 to 20 kg) or 20 (≥20 kg) mg Daily</p>	<p>Delayed-release capsule (OTC): 20.6 mg</p> <p>Delayed-release tablet (OTC): 20 mg</p> <p>Delayed-release suspension: 2.5 mg 10 mg</p>
<p>Omeprazole with sodium bicarbonate</p>	<p><u>Treatment of symptomatic GERD:</u> Capsule, powder for oral suspension: 20 mg Daily for 4 weeks</p> <p><u>Treatment of active duodenal ulcers:</u> Capsule, powder for oral suspension: 20 mg Daily for 4 weeks<sup>+++</sup></p> <p><u>Treatment of erosive esophagitis:</u> Capsule, powder for oral suspension: 20 mg Daily for 4 to 8 weeks</p> <p><u>Treatment of active, benign gastric</u></p>	<p>Safety and efficacy in children have not been established.</p>	<p>Capsule: 20 mg 40 mg</p> <p>Powder for oral suspension: 20 mg 40 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p><u>ulcer:</u> Capsule, powder for oral suspension: 40 mg Daily for 4 to 8 weeks</p> <p><u>Maintenance of healing of erosive esophagitis:</u> Capsule, powder for oral suspension: 20 mg once daily</p> <p><u>Risk reduction of upper gastrointestinal bleeding in critically ill patients:</u> Powder for oral suspension (40 mg/1,680 mg): initial, 40 mg; followed by 40 mg 6 to 8 hours later and 40 mg thereafter for 14 days</p>		
Pantoprazole	<p><u>Treatment of symptomatic GERD<sup>###</sup>:</u> Solution for injection: 40 mg Daily for 7 to 10 days</p> <p><u>Treatment of erosive esophagitis:</u> Delayed release suspension, delayed-release tablet: 40 mg Daily for up to 8 weeks<sup>****</sup></p> <p><u>Maintenance of healing of erosive esophagitis:</u> Delayed-release suspension, delayed-release tablet: 40 mg Daily</p> <p><u>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome:</u> Delayed-release suspension, delayed-release tablet: 40 mg BID<sup>†††</sup></p> <p>Solution for injection: 80 mg BID<sup>†††</sup></p>	<p><u>Treatment of erosive esophagitis in children ≥5 years of age:</u> Delayed-release suspension, delayed-release tablet: 20 (15 to 40 kg) or 40 (≥40 kg) mg Daily for up to 8 weeks</p>	<p>Delayed-release suspension: 40 mg</p> <p>Delayed-release tablet: 20 mg 40 mg</p> <p>Solution for injection: 40 mg</p>
Rabeprazole	<p><u>Treatment of symptomatic GERD:</u> Delayed-release tablet: 20 mg Daily for 4 weeks<sup>†</sup></p> <p><u>H pylori eradication to reduce the risk of duodenal ulcer recurrence:</u> Delayed-release tablets: 20 mg BID for 7 days<sup>†</sup></p> <p><u>Treatment of active duodenal ulcers:</u> Delayed-release tablet: 20 mg Daily for 4 weeks<sup>§§§§</sup></p> <p><u>Treatment of erosive esophagitis:</u> Delayed-release tablet: 20 mg Daily for 4 to 8 weeks<sup>   </sup></p>	<p><u>GERD in children ≥12 years:</u> Delayed-release tablet: 20 mg Daily for up to 8 weeks</p>	<p>Delayed-release tablet: 20 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p><u>Maintenance of healing of erosive esophagitis:</u> Delayed-release tablet: 20 mg Daily</p> <p><u>Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome:</u> Delayed-release tablet: 60 mg Daily<sup>¶¶¶¶</sup></p>		

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 9. Clinical Guidelines**

Clinical Guideline	Recommendations
<p>American College of Gastroenterology: <b>Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease (2005)</b><sup>19</sup></p>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• 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<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) given in divided doses may be effective in some patients with less severe GERD.</li> <li>• 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<sub>2</sub>RA-treated and 83% of PPI-treated patients. Esophagitis healed in 24% of placebo-treated, 50% of H<sub>2</sub>RA-treated and 78% of PPI-treated patients. Both higher doses and more frequent dosing of H<sub>2</sub>RAs appear to improve results in the treatment of reflux, but are still inferior to PPIs.</li> <li>• Continuous therapy to control symptoms and prevent complications is appropriate since GERD is a chronic condition.</li> </ul>
<p>American Gastroenterological Association: <b>Medical Position Statement on the Management of Gastroesophageal Reflux Disease (2008)</b><sup>20</sup></p>	<ul style="list-style-type: none"> <li>• 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<sub>2</sub>RAs, which are more effective than placebo.</li> <li>• Twice daily PPI therapy is recommended for patients who had an inadequate symptom response to once daily PPI therapy. There is no evidence of improved efficacy by adding a nocturnal dose of an H<sub>2</sub>RA to twice daily PPI therapy.</li> <li>• 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<sub>2</sub>RAs, which are more effective than placebo.</li> <li>• 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<sub>2</sub>RA.</li> <li>• 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</li> </ul>

Clinical Guideline	Recommendations
	<p>is the primary objective.</p> <ul style="list-style-type: none"> <li>Less than daily dosing of PPI therapy as maintenance therapy is not recommended in patients with an esophageal syndrome who previously had erosive esophagitis.</li> </ul>
<p>American College of Gastroenterology: <b>Guidelines for the Management of Dyspepsia (2005)</b><sup>21</sup></p>	<ul style="list-style-type: none"> <li>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 <i>Helicobacter pylori</i> (<i>H pylori</i>) prevalence is low (&lt;10%).</li> <li>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.</li> <li>In populations with a moderate to high prevalence of <i>H pylori</i> infection (≥10%), test and treat for <i>H pylori</i> and give a trial of acid suppression if eradication is successful but symptoms do not resolve.</li> <li>Dyspeptic patients &gt;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.</li> </ul>
<p>American Gastroenterological Association: <b>Medical Position Statement: Evaluation of Dyspepsia (2005)</b><sup>22</sup></p>	<ul style="list-style-type: none"> <li>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 <i>H pylori</i> testing and treatment of positive cases followed by acid suppression if symptoms remain. PPIs are the drug class of choice for acid suppression.</li> <li>Patients who are <i>H pylori</i> negative should be prescribed an empirical trial of acid suppression with a PPI for four to eight weeks.</li> <li>Empirical PPI therapy is the most cost-effective approach in populations with a low prevalence of <i>H pylori</i> (≤10%).</li> <li>Patients with dyspepsia who are &gt;55 years old or who have alarm features should have an esophagogastroduodenoscopy with biopsy for <i>H pylori</i>. Treatment should be targeted at the underlying diagnosis.</li> </ul>
<p>American College of Gastroenterology: <b>Guideline on the Management of <i>Helicobacter pylori</i> Infection (2007)</b><sup>23</sup></p>	<ul style="list-style-type: none"> <li>In the United States, the recommended primary therapies for <i>H pylori</i> infection include: a PPI, clarithromycin and amoxicillin or metronidazole (clarithromycin-based triple therapy) for 14 days for eradication rates of 70 to 85% or a PPI or H<sub>2</sub>RA, bismuth, metronidazole and tetracycline (bismuth-based quadruple therapy) for 10 to 14 days for eradication rates of 75 to 90%.</li> <li>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.</li> <li>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.</li> <li>In patients with persistent <i>H pylori</i> 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.</li> </ul>

Clinical Guideline	Recommendations
<p>European <i>Helicobacter pylori</i> Study Group:  <b>Current Concepts in the Management of <i>Helicobacter pylori</i> Infection—The Maastricht III Consensus Report (2007)</b><sup>24</sup></p>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Bismuth-based quadruple therapies (10 or 14 days) are alternative first-choice treatments.</li> <li>• Bismuth-based quadruple therapies remain the best second-choice treatment. If not available, a PPI, amoxicillin or tetracycline and metronidazole are recommended.</li> </ul>
<p>American College of Gastroenterology:  <b>Updated Guidelines 2008 for the Diagnosis, Surveillance and Therapy of Barrett's Esophagus (2008)</b><sup>25</sup></p>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• Screening for Barrett's esophagus remains controversial because of the lack of documented impact on mortality from esophageal adenocarcinoma.</li> <li>• The grade of dysplasia determines the appropriate surveillance interval. Any grade dysplasia by histology should be confirmed by an expert pathologist.</li> <li>• Low grade dysplasia requires expert pathologist confirmation and more frequent endoscopy and biopsy.</li> <li>• 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.</li> <li>• Any mucosal irregularity (e.g., nodularity, ulcer) is best assessed with endoscopic resection for a more extensive histologic evaluation and exclusion of cancer.</li> <li>• Management of patients with high grade dysplasia is dependent on local expertise, both endoscopic and surgical and the patient's age, comorbidity and preferences.</li> <li>• No biomarkers or panel is currently ready for routine clinical use.</li> <li>• Chemoprevention represents a promising future strategy.</li> <li>• The goal of pharmacologic acid suppression with agents such as PPIs is to control reflux symptoms.</li> <li>• Reflux symptoms can be controlled in most patients with PPI therapy; twice daily dosing may be necessary in a subgroup of patients.</li> <li>• There is currently no data that directly support the use of high dose antisecretory therapy to delay or prevent the development of esophageal adenocarcinoma.</li> <li>• Patients who are optimal candidates for surgery may elect fundoplication, including patients lacking major comorbidity and whose reflux symptoms are controlled with PPI therapy.</li> <li>• The vast majority of data do not provide support that fundoplication prevents esophageal adenocarcinoma.</li> </ul>
<p>American College of</p>	<ul style="list-style-type: none"> <li>• Patients requiring nonsteroidal anti-inflammatory drug (NSAID) therapy</li> </ul>

Clinical Guideline	Recommendations
Gastroenterology: <b>Guidelines for Prevention of Nonsteroidal Anti-inflammatory Drugs- Related Ulcer Complications (2009)</b> <sup>26</sup>	<p>who are at high risk (e.g., prior ulcer bleeding) should receive alternative therapy, or if anti-inflammatory treatment is absolutely necessary, a cyclooxygenase (COX)-2 inhibitor, and cotherapy with misoprostol or high-dose PPI.</p> <ul style="list-style-type: none"> <li>• Patients at moderate risk can be treated with a COX-2 inhibitor alone or with a traditional nonselective NSAID plus misoprostol or a PPI.</li> <li>• Patients at low risk can be treated with a nonselective NSAID.</li> <li>• 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.</li> <li>• 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.</li> <li>• High-dose H<sub>2</sub>RAs are more effective than placebo in reducing the risk of NSAID-induced endoscopic peptic ulcers; however, the H<sub>2</sub>RAs are significantly less effective than PPIs.</li> </ul>

### Conclusions

Proton-pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion available.<sup>1</sup> 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.<sup>8-18</sup> 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 magnesium 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.<sup>28-57</sup> 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.<sup>28,30,32,34,35,38,40,43,44</sup> 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.<sup>49</sup> 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.<sup>28,30,32,34,35,36,40,43,44</sup> Subgroup analyses in a few trials noted better healing rates with esomeprazole in patients with more severe disease.<sup>41,43</sup> 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.<sup>31,33,39,42,45,47</sup> It should be noted that most trials that compared esomeprazole to omeprazole employed doses of 40 mg for esomeprazole and 20 mg for omeprazole.<sup>28,30,38,40</sup> 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.<sup>58</sup> 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.<sup>59-74</sup> 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.<sup>64</sup> A few studies have noted higher eradication rates of *H pylori* in patients who were poor metabolizers of PPIs.<sup>3,27</sup> 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  $\leq 55$  years and no alarm features), and peptic ulcer disease caused by NSAID therapy.<sup>19-22,26</sup> Triple and quadruple combination therapy with antibiotics and a PPI are considered first-line therapy for peptic ulcer disease caused by *H pylori*.<sup>23,24</sup> None of the treatment guidelines recommend one PPI over another or one formulation of a PPI over another.<sup>18-26</sup>

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.

**Appendix I: Utilization Within this Drug Class for DVHA: April 1, 2010 to September 30, 2010**

Medication	Unique Utilizers	# of Claims	% Marketshare	Amount Paid	Avg Cost/Claim
Prilosec OTC	4,708	8,798	47.75%	\$334,279.87	\$37.99
Protonix	3,091	5,066	27.50%	\$1,631,423.33	\$322.03
Kapidex/Dexilant	2,159	2,457	13.34%	\$657,240.27	\$267.50
Prevacid Solutab	503	802	4.35%	\$274,731.81	\$342.56
Nexium	320	540	2.93%	\$249,857.56	\$462.70
Omeprazole	239	332	1.80%	\$11,855.12	\$35.71
Prevacid	159	256	1.40%	\$123,862.48	\$483.84
Aciphex	46	62	0.34%	\$34,763.22	\$560.70
Pantoprazole	31	63	0.34%	\$13,170.87	\$209.06
Lansoprazole	18	43	0.23%	\$22,478.70	\$522.76
Prilosec	6	6	0.03%	\$5,094.41	\$849.07
<b>Class Total:</b>	<b>11,310</b>	<b>18,425</b>	<b>100%</b>	<b>\$3,358,757.64</b>	<b>\$182.29</b>

**Recommendations**

In recognition of the well-established role of the single entity proton-pump inhibitors (PPIs) for the treatment of gastrointestinal disorders, the extended track record of efficacy and safety of these agents, comparable safety and efficacy profiles of all agents in the class and the availability of several generic proton-pump inhibitors, no changes are recommended to the current Department of Vermont Health Access (DVHA) approval criteria (see below).

**lansoprazole ODT, Nexium powder for suspension, Prevacid Solutabs (for patients  $\geq$  12 years old), Prilosec packet, Protonix packet**

- The patient has a requirement for an oral liquid dosage form. In addition, for approval of lansoprazole ODT, the patient has a documented intolerance to brand Prevacid Solutabs.

**Other non-preferred medications:**

- The member has had a documented side effect, allergy, or treatment failure to Kapidex/Dexilant capsules, omeprazole RX 20 mg or 40 mg generic capsules AND Protonix tablets.
- If the request is for Prevacid 24 hr OTC or lansoprazole generic RX capsules, the patient must also have a documented intolerance to brand Prevacid RX.

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