Proton Pump Inhibitors Review

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FDA-Approved Indications (adults)[1,2,3,4,5,6,7]

Drug	Manufacturer	Duodenal Ulcer		Pyrosis (Heartburn)	*H. pylori* eradication	GERD	Erosive Esophagitis		Pathological hypersecretory conditions	Gastric ulcers	NSAID-induced gastric ulcers
		Treatment	Maintenance				Treatment	Maintenance			
dexlansoprazole (Dexilant™)*	Takeda	--	--	--	--	X	X	X	--	--	--
esomeprazole (Nexium®)	Astra-Zeneca	--	--	--	X with amoxicillin + clarithromycin	X	X	X	X	--	X (risk reduction)
lansoprazole (Prevacid®)	generic, Takeda	X	X	--	X with amoxicillin +/- clarithromycin	X	X	X	X	X	X (risk reduction, healing)
lansoprazole OTC (Prevacid 24-HR)	Novartis	--	--	X	--	--	--	--	--	--	--
omeprazole (Prilosec®)	generic, Astra-Zeneca	X	--	--	X with clarithromycin +/- amoxicillin	X	X	X	X	X	--
omeprazole magnesium OTC (Prilosec OTC®)	generic, Procter & Gamble	--	--	X	--	--	--	--	--	--	--
omeprazole OTC	Dexcel	--	--	X	--	--	--	--	--	--	--
omeprazole/ sodium bicarbonate (Zegerid®)	generic, Santarus	X	--	--	--	X	X	X	--	X	--
omeprazole/sodium bicarbonate OTC (Zegerid OTC)	Santarus/ Merck	--	--	X	--	--	--	--	--	--	--
pantoprazole (Protonix®)	generic, Wyeth	--	--	--	--	--	X	X	X	--	--
rabeprazole (Aciphex®)	Eisai	X	--	--	X with amoxicillin + clarithromycin	X	X	X	X	--	--

- Omeprazole/sodium bicarbonate (Zegerid) 40/1,680 mg is indicated for the reduction of risk of upper GI bleeding in critically ill patients.
- Esomeprazole (Nexium) is indicated for the short-term treatment of GERD in children one to 17 years old.
- Lansoprazole (Prevacid) is indicated for the short-term treatment of GERD in children older than one year and the short term treatment of erosive esophagitis in children one to 11 years old.
- Omeprazole (Prilosec) is indicated for the treatment of GERD and maintenance of healing of EE in children one to 16 years.
- Rabeprazole (Aciphex) is indicated for the short-term treatment of GERD in children 12 years of age and older.
- Pantoprazole (Protonix) is indicated for short-term treatment of erosive esophagitis associated with GERD in children ages five years and older.
- The manufacturer of Zegerid does not participate in the CMS Federal Rebate Program at this time.
- *Takeda announced that dexlansoprazole (Kapidex) is now marketed in the United States under the new product trade name DEXILANT™ effective in April 2010. This change is to prevent medication errors related to similar medication names.

Overview

Proton pump inhibitors (PPIs) demonstrate gastric acid suppression superior to histamine-2 receptor antagonists (H_2RAs). PPIs achieve a more rapid and sustained increase in gastric pH and are not associated with the rapid tachyphylaxis seen with H_2RAs, thereby, offering improved treatment of various acid-peptic disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathy. PPIs have minimal adverse effects, few significant drug interactions, and are generally considered safe for long-term treatment.[8]

PPIs are recommended as first-line therapy for the treatment of severe GERD-related symptoms or erosive esophagitis (EE). H_2RAs can be used in patients with mild symptoms or verified nonerosive disease. Acid suppression is the mainstay of therapy for GERD. PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients.

The 2008 American Gastroenterological Association Medical Position Statement on the Management of Gastroesophageal Reflux Disease state that for healing esophagitis and symptomatic relief, PPIs are more effective than H-2 receptor antagonists, and H-2 receptor antagonists are more effective than placebo.[9] Good data in support of using higher than standard doses of these drugs are not available. There is no clinical trial evidence examining the use of twice daily PPI dosing in patients who have an unsatisfactory response to once-daily dosing. However, expert opinions almost unanimously recommend twice daily dosing in these patients. Failure of twice daily dosing should be considered a treatment failure. Patients with suspected reflux chest pain syndrome (after a cardiac etiology has been carefully evaluated) may be given a four-week trial of twice daily PPI therapy. If this fails to resolve symptoms, further diagnostic testing is recommended. Patients with erosive esophagitis have high recurrence rates if not maintained on chronic PPI therapy. Those with esophageal GERD syndrome without esophagitis are less likely to have recurrence. If symptoms recur, an on-demand PPI regimen is a reasonable strategy to control symptoms. There is inadequate evidence to recommend routine bone density studies, calcium supplementation or *H pylori* screening because of PPI use.

PPIs are used in conjunction with various antimicrobials for the eradication of *Helicobacter pylori*, the most common cause of PUD. Antisecretory therapy with either H_2RAs or PPIs accelerates ulcer healing and provides rapid symptomatic improvement. However, failure to eradicate *H. pylori* results in a 60 to 80 percent relapse rate after one year in the absence of continual maintenance antisecretory therapy.[10] The rates of relapse following successful eradication of *H. pylori* range from 0.5 percent to up to 20 percent.[11,12]

NSAID use, the second-most common cause of PUD, is largely responsible for the current epidemic of upper gastrointestinal (GI) bleeding and perforation in the elderly. Continued NSAID use may delay healing of ulcers.[13] PPIs are as effective as misoprostol at reducing NSAID-induced ulcer formation and are better tolerated.[14,15]

The 2008 Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/ACG/AHA) identify a preventive role of PPIs in NSAID- and Antiplatelet Drug-Related GI Events.[16] NSAIDs (traditional and COX-2 inhibitors) increase the risk of cardiovascular and cerebrovascular events. The authors refer to an AHA scientific statement on the use of NSAIDs in patients with known cardiovascular disease or risk factors for ischemic heart disease (2007) for recommendations on drug selection for the management of musculoskeletal pain in these patients. Patients at risk for gastrointestinal events who require NSAID therapy (either a traditional NSAID or a COX-2 inhibitor) and a cardioprotective dose of

ASA (≤ 325 mg/day) should receive a gastrointestinal protective agent (e.g., PPI). Patients requiring combination treatment with ASA and anticoagulants (unfractionated heparin, low-molecular weight heparin, or warfarin) should receive concomitant PPIs. Additionally, PPIs are the preferred agents for the therapy and prophylaxis of NSAID- and ASA-associated GI injury. The usefulness of misoprostol is limited by its side effect profile. Traditional doses of H_2 receptor antagonists do not prevent most NSAID-related gastric ulcers,1 and there are little data on their use in conjunction with ASA.

According to the 2008 guidelines of the American Gastroenterological Association (AGA) Institute, there were several strongly recommended options based on good evidence that may improve important health outcomes in the treatment of patients with esophageal GERD syndromes.[17] One of these options is that healing esophagitis, symptomatic relief, and maintaining healing of esophagitis are more effective with PPIs than H_2RAs. Long-term use of PPIs for the treatment of patients with esophagitis is reasonable as long as the dose is titrated down to the lowest effective dose based on symptom control. Lastly, antireflux surgery should remain an option if a patient is intolerant of acid suppressive therapy.

The 2005 Guidelines for the Management of Dyspepsia state that in *H. pylori*-negative cases with uninvestigated dyspepsia and no alarm features, an empiric trial of acid suppression for four to eight weeks is recommended as first-line therapy. [18] A short course of PPI therapy has demonstrated better symptom control than therapy with H_2 receptor antagonists in a meta-analysis of large studies. The interpretation of these results is complicated by the inclusion of patients with symptomatic reflux and peptic ulcers. PPIs are the preferred agent for acid suppression for dyspepsia in ACG guidelines. In areas with *H. pylori* prevalence greater than 10 percent, patients should be tested and treated for *H. pylori* before an acid suppression trial. For patients who respond to initial therapy, treatment should be stopped after four to eight weeks. Long-term empiric antisecretory therapy may lead to inappropriate maintenance therapy that the patient does not require. Long-term empiric antisecretory therapy may result in inappropriately and inadequately treated peptic ulcer disease. Peptic ulcer disease may also be misdiagnosed in cases where ulcers are healed to a point that they cannot be identified during endoscopy. Another course of the same treatment should be provided if symptoms relapse.

The 2005 Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease indicate that PPIs eliminate symptoms and heal esophagitis more frequently and more rapidly than other agents, including H_2 receptor antagonists.[19] PPIs are safe and effective. The benefits of chronic PPI therapy in patients with chronic or complicated GERD outweigh any risks. PPIs should always be dosed prior to meals, and most patients on once daily PPI therapy should take the dose before breakfast. In some situations, it is reasonable to use higher than approved doses of PPIs, which may be given as a divided dose. This is particularly beneficial in cases of diagnostic trial of non-cardiac chest pain, empiric treatment trial for supraesophageal symptoms of GERD, patients with a partial response to standard dose therapy, patients who have responded to therapy but continue to have breakthrough symptoms, patients with severe esophageal dysmotility, and patients with Barrett's esophagus. PPI therapy results in the best symptom control and esophagitis healing among the available medical options. The only advantage to using less effective therapy is potential cost savings. These guidelines also state that on-demand therapy with PPIs has not been well studied, but this practice may be cost effective in patients with mild-to-moderate symptoms. Once a patient has failed less effective therapy, they should have access to chronic PPI therapy. Improvement in GERD symptoms noted with acid suppression by full dose PPI therapy is usually followed by rapid return of symptoms once PPI therapy is discontinued. Many patients with GERD require long-term (possibly life-long) therapy. Additionally, reflux symptoms related to Barrett's Esophagus can be

controlled in most patients with PPI therapy. Twice a day dosing may be necessary in a subgroup of patients. Lastly, PPIs may be useful in the prevention of NSAID-related ulcer complications. Patients requiring NSAID therapy who are at high risk for gastric ulcers (e.g., prior ulcer bleeding or multiple GI risk factors) should receive a COX-2 inhibitor in combination with misoprostol or high-dose PPI. NSAID therapy should only be used when absolutely necessary in these patients. Patients at moderate risk for GI ulcers can be treated with a COX-2 inhibitor alone or with a traditional nonselective NSAID plus misoprostol or a PPI.

Pharmacology

All PPIs are substituted benzimidazole derivatives that reduce gastric acid secretion by specifically inhibiting the proton pump (H^+/K^+-ATPase) at the secretory surface of the gastric parietal cell.[20,21,22]

PPIs are prodrugs, which require activation in order to inhibit gastric acid secretion. After oral administration, PPIs are absorbed into systemic circulation and ultimately enter actively secreting parietal cells. At highly acidic pH, the agents are activated by conversion to a sulfenamide moiety that binds to the luminal surface of H^+/K^+-ATPase, thereby irreversibly inhibiting the gastric proton pump.[23,24] A profound, long-lasting antisecretory effect is produced, capable of maintaining the gastric pH above 4, even during postprandial acid surges.[25]

Pharmacokinetics

Drug	Bioavailability (%)	$t_{1/2}$ (hours)	T_{max} (hours)	Metabolism	Elimination (%)
dexlansoprazole (Dexilant)[26]	47-60	1-2	1-2 then 4-5	Hepatic by CYP 3A4, 2C19 to inactive metabolites Metabolism of active drug is nearly 100 percent	Urine: 50.7 Feces: 47.6
esomeprazole (Nexium)[27]	64-90	1.0-1.5	1.5		Urine: 80 Feces: 20
lansoprazole (Prevacid)[28]	80	< 2	1.7		Urine: 33 Feces: 67
omeprazole (Prilosec)[29]	30-40	0.5-1	0.5-3.5		Urine: 77 Feces: 23
omeprazole/ sodium bicarbonate (Zegerid)[30]	30-40	1	0.5		Urine: 77 Feces: 23
pantoprazole (Protonix)[31]	77	1	2.5		Urine: 71 Feces: 18
rabeprazole (Aciphex)[32]	52	1-2	2-5		Urine: 90 Feces: 10

PPIs are degraded by gastric acid. Drug formulations must therefore withstand degradation to deliver active drug to the stomach for absorption. Pharmacokinetic studies indicate plasma concentrations vary considerably from individual to individual, and there is poor correlation

between maximal plasma concentration and degree of gastric acid suppression.[33,34] Although PPIs have short plasma elimination half-lives, duration of gastric acid inhibition is prolonged due to irreversible binding to the proton pump.[35] With continued daily dosing, bioavailability increases for esomeprazole and omeprazole.[36,37]

Genetic expression of CYP2C19 varies from person to person. As a result, a small subset of patients (13 to 23 percent of Asians, two to six percent of Caucasians) experience two to four times higher than usual plasma concentrations when treated with PPIs extensively metabolized by CYP2C19.[38] The metabolism of rabeprazole is less dependent on CYP2C19 and therefore may be less affected by this genetic polymorphism.

Some claim that a dose of 40 mg of the S-enantiomer of omeprazole (esomeprazole) results in 10 to 15 percent higher healing rates in GERD patients, compared to 20 mg omeprazole racemate. The same difference in healing rate is found when the two doses of omeprazole racemate are compared to each other. Moreover, as with the other PPIs, pharmacokinetic differences between the enantiomers seem to be of little, if any, clinical importance in the patient.[39]

Contraindications/Warnings[40,41,42,43,44,45,46,47]

PPIs are contraindicated in patients with known hypersensitivity to any component of the formulation.

A special precaution related to the phenylalanine component in lansoprazole orally disintegrating tablet (ODT) (Prevacid SoluTab) for patients with phenylketonuria is listed. There is 2.5 mg of phenylalanine in the 15 mg tablet and 5.1 mg in the 30 mg tablet.

Symptomatic response to therapy with PPIs does not preclude the presence of gastric malignancy.

The sodium content of omeprazole/sodium bicarbonate (Zegerid) products should be considered when prescribing to patients on a sodium restricted diet. The powder for oral suspension formulation contains 1,680 mg (20 mEq, 460 mg Na+) of sodium bicarbonate and the capsules contain 1,100 mg (13 mEq, 304 mg Na+) per capsule. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, respiratory alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. Based on several published observational studies, the risk of fracture was increased in patients who received high-dose PPIs, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines.

On March 2, 2011, the FDA notified healthcare professionals and the public that prescription PPIs may cause hypomagnesemia if taken for prolonged periods of time (in most cases, longer than one year).[48] Low serum magnesium levels can result in serious adverse events including muscle spasm (tetany), irregular heartbeat (arrhythmias), and convulsions (seizures); however, patients do not always have these symptoms. Treatment of hypomagnesemia generally requires magnesium supplements. In approximately one-quarter of the cases reviewed, magnesium

supplementation alone did not improve low serum magnesium levels, and the PPI had to be discontinued. Healthcare professionals should consider obtaining serum magnesium levels prior to initiation of prescription PPI treatment in patients expected to be on these drugs for long periods of time, as well as patients who take PPIs with medications such as digoxin, diuretics, or drugs that may cause hypomagnesemia.

Drug Interactions[49,50,51,52,53,54,55]

All PPIs have the potential to cause pH-dependent drug interactions. The agents can cause a significant decrease in the absorption of weak bases such as ketoconazole or itraconazole.

Omeprazole (Prilosec, Prilosec OTC, Zegerid) inhibits CYP2C19, potentially leading to interactions with diazepam, phenytoin, and warfarin.

Effects of esomeprazole (Nexium) on CYP2C19 have not been shown to be clinically relevant. Lansoprazole (Prevacid) weakly induces the metabolism of theophylline. In contrast, rabeprazole (Aciphex), dexlansoprazole (Dexilant), and pantoprazole (Protonix) do not interact with the CYP450 system significantly.

Atazanavir (Reyetaz®) and nelfinavir (Viracept®), HIV protease inhibitors, require the presence of gastric acid for absorption; therefore, PPIs reduce gastric acid and systemic absorption of atazanavir and nelfinavir. PPIs should not be coadministered with these agents. In addition, omeprazole and esomeprazole may increase the plasma levels of saquinavir (Invirase®). Dose reduction of saquinavir should be considered from the safety perspective for individual patients.

Concomitant administration of omeprazole, lansoprazole, or dexlansoprazole with tacrolimus may increase the serum levels of tacrolimus.

Concurrent use of PPIs and warfarin may result in increased INR and prothrombin time which may lead to abnormal bleeding and even death. In studies, coadministration of dexlansoprazole or lansoprazole with warfarin did not affect the pharmacokinetics of warfarin nor were significant changes in INR identified. The INR in patients treated with all PPIs and warfarin concomitantly should be monitored.

Co-administration of clopidogrel with omeprazole 80 mg reduces the pharmacological activity of clopidogrel if given concomitantly or if given 12 hours apart. In a Health Professionals Update released in November 2009, the FDA suggests that the other acid-reducing drugs esomeprazole and cimetidine also be avoided because they may have a similar effect.[56,57,58] The FDA states that there is insufficient information about the use of clopidogrel and other PPIs to make recommendations about their coadministration. The FDA states that there is no evidence that other H-2 receptor antagonists or antacids interfere with clopidogrel. A warning has been added to the clopidogrel label advising against concomitant use of clopidogrel and CYP 2C19 inhibitors (e.g., omeprazole, esomeprazole). The label advises consideration of using another acid-reducing agent with less CYP 2C19 inhibitory activity and notes that pantoprazole is a weak inhibitor of CYP 2C19 with less effect on clopidogrel's antiplatelet activity.

According to an Expert Consensus Document released in November 2010 jointly by the American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG), and the American Heart Association (AHA), using PPIs and antiplatelet drugs (thienopyridines) together is an appropriate way of treating patients with cardiovascular disease who are at high risk of upper gastrointestinal (GI) bleeds, despite recent concerns about an

adverse interaction between these two types of drugs.[59] Use of antiplatelet drugs increases the risk of upper GI bleeding from pre-existing ulcers, lesions, and other tissue breaks in the GI tract. Those at highest risk for GI bleeding are patients with a history of previous GI bleeding, as well as patients with multiple risk factors for upper GI bleeding, including: a history of peptic ulcer disease; advanced age; use of anticoagulants, steroids, or NSAIDs; and *H. pylori* infection.

Combined administration consisting of rabeprazole or esomeprazole with amoxicillin and clarithromycin resulted in increases in plasma concentrations of rabeprazole and 14-hydroxyclarithromycin. Similar was reported with the co-administration of omeprazole and clarithromycin.

Voriconazole (Vfend®), a combined inhibitor of CYP2C19 and CYP3A4, may lead to a two-fold increase in plasma levels of omeprazole and esomeprazole. Dose adjustment of the PPI is not normally required. However, in patients with Zollinger-Ellison syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered.

Adverse Effects[60]

Drug	Abdominal pain	Diarrhea	Headache	Nausea
dexlansoprazole (Dexilant)[61]	3.5 – 4.0	4.7 – 5.1	< 2.0	2.8 – 3.3
esomeprazole (Nexium)[62]	3.8	4.3	3.8 - 5.5	> 1.0
lansoprazole (Prevacid)[63]	2.1	1.4 - 7.4	≥1	1.3 - 3.0
omeprazole (Prilosec)[64]	5.2	3.7	6.9	4.0
omeprazole/sodium bicarbonate (Zegerid)[65]	0.4 - 5.2	1.9 - 3.7	2.4 - 6.9	0.9 - 4.0
pantoprazole (Protonix)[66]	1 – 4	2 - 6	2 - 9	2
rabeprazole (Aciphex)[67]	< 2	< 2	< 2	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported

The Food and Drug Administration (FDA) completed a comprehensive, scientific review of the known safety data for omeprazole and esomeprazole on December 10, 2007. The difference in the frequency of heart attacks and other heart-related problems seen in an earlier analysis of the two small long-term studies does not indicate the presence of a true effect. Therefore, the FDA concluded that the long-term use of these drugs is not likely to be associated with an increased risk of heart problems. Based on everything now known at the agency, the FDA recommends that health care providers continue to prescribe, and patients continue to use, these products as described in their labeling.[68]

Special Populations[69,70,71,72,73,74,75]

Pediatrics

Safety and effectiveness of lansoprazole (Prevacid) have been established for the short-term treatment of GERD and short-term treatment of erosive esophagitis in children aged one to 17 years. Esomeprazole (Nexium) is indicated for short-term treatment of GERD (ages one to 17 years) and the healing of erosive esophagitis (ages one to 11 years). Omeprazole (Prilosec) is indicated for children ages one to 16 years for the short-term treatment of GERD and the maintenance of healing of erosive esophagitis. Rabeprazole (Aciphex) is indicated for the short-term treatment of GERD in patients 12 years of age and older. Pantoprazole (Protonix) is indicated in children five years of age and older for the short-term treatment in the healing and symptomatic relief of erosive esophagitis.

Safety and effectiveness of dexlansoprazole (Dexilant) have not been established in patients less than 18 years of age. No adequate well-controlled studies in pediatric patients have been performed for omeprazole/sodium bicarbonate (Zegerid).

Pregnancy

Omeprazole (Prilosec, Zegerid) is Pregnancy Category C. Other agents in the class are rated Pregnancy Category B.

Other considerations – renal, hepatic, race, etc.

The clearance of PPIs may be reduced in patients with advanced age and those with mild to moderate liver disease.[76,77,78] The decrease in clearance, however, does not necessitate a dose reduction. Pharmacokinetic studies in patients with severe liver disease indicate there is a substantial increase in the area under the concentration-time curve and a prolongation of the plasma elimination half-life for every PPI.[79,80] The half-life does not reflect the duration of suppression of gastric acid secretion caused by PPIs.

Consideration should be given to reducing PPI dosage in patients with severe hepatic disease. Doses of dexlansoprazole (Dexilant) 30 mg should be considered for patients with moderate hepatic disease; however, no studies have been conducted with dexlansoprazole in patients with severe hepatic impairment. Doses of esomeprazole (Nexium) should not exceed 20 mg in those with severe hepatic disease. Doses of pantoprazole (Protonix) greater than 40 mg per day have not been studied in patients with severe hepatic impairment.

Dose reduction is not required in patients with renal impairment due to significant metabolism of PPIs by the liver.

Genetic expression of CYP2C19 varies from person to person. As a result, a small subset of patients (13 to 23 percent of Asians, two to six percent of Caucasians) experience two to four times higher than usual plasma concentrations when treated with PPIs extensively metabolized by CYP2C19.

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in area under the curve (AUC) of approximately four-fold was noted in Asian subjects compared with Caucasians. Dose reduction, particularly where maintenance of healing of erosive esophagitis is indicated, for Asian subjects should be considered.

Dosages

Drug	Adults	Pediatrics	Oral Availability
dexlansoprazole (Dexilant)[81]	Erosive esophagitis (healing) – 60 mg once daily for up to eight weeks	--	30, 60 mg delayed-release capsules
	Erosive esophagitis (maintenance of healing) – 30 mg once daily (Controlled studies did not extend beyond six months.)		
	Symptomatic non-erosive GERD – 30 mg once daily for four weeks		
esomeprazole (Nexium)[82]	*H. pylori* eradication - 40 mg daily + clarithromycin 500 mg and amoxicillin 1 g twice daily for 10 days	Erosive Esophagitis (treatment) - Ages one to 11 years: Weight-based dosing < 20 kg: 10 mg daily for eight weeks ≥ 20 kg: 10 to 20 mg daily for eight weeks GERD – Ages one to 11 years: 10 mg daily for up to eight weeks GERD - Ages 12 to 17 years: 20 to 40 mg daily for up to eight weeks	20, 40 mg delayed-release capsules 10, 20, 40 mg delayed-release powder for oral suspension* Nexium Delayed-Release Powder for Oral Suspension should be administered in water.
	GERD - 20 or 40 mg daily for four weeks. An additional four weeks may be considered if needed.		
	Erosive esophagitis (treatment) - 20 or 40 mg daily for four weeks. An additional four weeks may be considered if needed.		
	Erosive esophagitis (maintenance) - 20 mg daily. (Controlled studies did not extend beyond six months.)		
	Pathological hypersecretory conditions - 40 mg twice daily		
	Reduction of risk for NSAID-associated gastric ulcers - 20 or 40 mg daily for up to six months.		

Dosages (Continued)

Drug	Adults	Pediatrics	Oral Availability
lansoprazole (Prevacid)[83]	Duodenal ulcer (treatment) - 15 mg daily for four weeks	GERD and Erosive esophagitis (treatment) - Ages one to 11 years: Weight-based dosing ≤ 30 kg: 15 mg daily for up to 12 weeks; > 30 kg: 30 mg daily for up to 12 weeks GERD - Ages 12 to 17 years: 15 mg daily for up to eight weeks Erosive Esophagitis (treatment) - Ages 12 to 17 years: 30 mg daily for up to eight weeks	15, 30 mg delayed-release capsules 15, 30 mg delayed-release orally disintegrating tablets
	Duodenal ulcer (maintenance) - 15 mg daily		
	H. pylori eradication – 30 mg twice daily + clarithromycin 500 mg and amoxicillin 1 g twice daily for 10-14 days OR 30 mg three times a day + amoxicillin 1 g three times a day for 14 days		
	Gastric ulcer – 30 mg daily for up to eight weeks		
	GERD – 15 mg daily for up to eight weeks		
	Erosive esophagitis (treatment) - 30 mg daily for up to eight weeks. An additional eight weeks may be considered if needed.		
	Erosive esophagitis (maintenance) – 15 mg daily		
	Pathological hypersecretory conditions - 60 mg 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 dose of greater than 120 mg should be administered in divided doses. Some patients with Zollinger-Ellison Syndrome have been treated continuously for more than four years.)		
	Reduction of risk of NSAID-associated gastric ulcers in patients who require a NSAID and have a history of gastric ulcer – 15 mg daily for up to 12 weeks		
	Healing of NSAID-associated gastric ulcers in patients who require a NSAID – 30 mg daily for up to eight weeks		
lansoprazole (Prevacid 24hr)	Heartburn - 15 mg daily for 14 days	--	15 mg delayed-release tablet

Dosages (Continued)

Drug	Adults	Pediatrics	Oral Availability
omeprazole (Prilosec)[84]	Duodenal ulcer (Treatment) - 20 mg daily for up to four to eight weeks	GERD (treatment) and Erosive Esophagitis (maintenance) Ages one to 16 years old: Weight based dosing 5 kg to < 10kg: 5 mg once daily 10kg to < 20 kg: 10 mg daily ≥ 20 kg: 20 mg daily Note: On a per kg basis, the doses to heal erosive esophagitis in pediatric patients are greater than those for adults.	10, 20, 40 mg delayed-release capsules 2.5, 10 mg packets for oral suspension Prilosec for Delayed-Release Oral Suspension should be administered in water.
	H. pylori eradication: Triple Therapy - 20 mg twice daily + clarithromycin 500 mg and amoxicillin 1 g twice daily for 10 days –OR- Dual Therapy - 40 mg daily + clarithromycin 500 mg three times a day for 14 days An additional 14 days (triple therapy) or 18 days (dual therapy) of omeprazole 20 mg daily is recommended for ulcer healing and symptom relief		
	Gastric ulcer - 40 mg daily for four to eight weeks		
	GERD- 20 mg daily for up to four weeks		
	Erosive esophagitis (treatment) - 20 mg daily for four to eight weeks		
	Erosive esophagitis (maintenance) - 20 mg daily		
	Pathological hypersecretory conditions - 60 mg daily (Doses up to 120 mg three times a day has been used. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with Prilosec for more than five years.)		
omeprazole magnesium OTC (Prilosec OTC)	Heartburn - 20 mg daily for 14 days	--	20 mg delayed-release tablet
omeprazole OTC			

Dosages (Continued)

Drug	Adults	Pediatrics	Oral Availability
omeprazole/ sodium bicarbonate (Zegerid)[85]	Duodenal ulcer (treatment) - 20 mg daily for four weeks. An additional four weeks may be considered if needed. Gastric ulcer - 40 mg daily for four to eight weeks GERD - 20 mg daily for up to four weeks Erosive esophagitis (treatment) - 20 mg daily for four to eight weeks Erosive esophagitis (maintenance) - 20 mg daily Reduction of risk of upper GI bleeding in critically ill patients (40 mg oral suspension only) - 40 mg initially, followed by 40 mg six to eight hours later and 40 mg daily thereafter for 14 days	--	20 and 40 mg immediate-release capsules (Each capsule contains 1,100 mg sodium bicarbonate) 20 and 40 mg immediate-release (Each packet contains 1,680 mg sodium bicarbonate) The 20 mg formulations contain the same amount of sodium bicarbonate as the 40 mg strengths, therefore two 20 mg doses are not equivalent to one 40 mg dose Capsules should be swallowed intact with water. Do not use other liquids. Do not open capsule and sprinkle contents into food. Contents of packet should be taken in 1-2 tablespoons of water. Do not use other liquids or foods.
omeprazole/ sodium bicarbonate OTC (Zegerid OTC)	Heartburn – one capsule daily for 14 days. An additional 14 day course may be repeated every four months.	--	20 mg/ 1,100 mg capsules
pantoprazole (Protonix)[86]	Erosive esophagitis (treatment) due to GERD - 40 mg daily for up to eight weeks. An additional eight weeks may be considered if needed. Erosive esophagitis (maintenance) due to GERD - 40 mg daily Pathological hypersecretory conditions - 40 mg twice daily (Dosages up to 240 mg daily have been used. Some patients have been treated continuously for more than two years.)	Short-term treatment of erosive esophagitis associated with GERD: Children (5 years and older): ≥ 15 kg to < 40 kg: 20 mg once daily up to eight weeks ≥ 40 kg: 40 mg once daily up to eight weeks	20, 40 mg delayed-release tablets 40 mg delayed-release packets for oral suspension Protonix For Delayed-Release Oral Suspension should only be administered in apple juice or applesauce, not in water or other liquids or foods. See package insert for complete administration directions.

Dosages (Continued)

Drug	Adults	Pediatrics	Oral Availability
rabeprazole (Aciphex)[87]	Duodenal ulcer (treatment) - 20 mg daily for up to four weeks. A few patients may require additional therapy to achieve healing.	GERD - Ages 12 years and older: 20 mg daily for up to eight weeks	20 mg delayed-release tablets
	H. pylori eradication - 20 mg twice daily + clarithromycin 500 mg and amoxicillin 1 g twice daily for seven days		
	GERD - 20 mg daily for four weeks. An additional four weeks may be considered if needed.		
	Erosive esophagitis (treatment) - 20 mg daily for four to eight weeks. An additional eight weeks may be considered if needed.		
	Erosive esophagitis (maintenance) - 20 mg daily		
	Pathological hypersecretory conditions - 60 mg daily (Doses up to 100 mg daily and 60 mg twice daily have been used. Some patients with Zollinger-Ellison syndrome have been treated continuously for up to one year.)		

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

For purposes of this review, data were further screened based on the following characteristics: open-label design, duration of therapy of less than three days, primary outcome studied not of clinical relevance, use of formulations not included in this review, unapproved dosing regimens, and results measured by survey.

Duodenal Ulcer

lansoprazole (Prevacid) versus omeprazole (Prilosec)

In a double-blind, randomized study, 279 patients with active duodenal ulcers were treated with either 30 mg lansoprazole or 20 mg omeprazole daily.[88] No differences in healing rates between

the groups either after two weeks (86.2 percent for lansoprazole and 82.1 percent for omeprazole) or after four weeks (97.1 percent and 96.2 percent, respectively) were observed. No patient ceased treatment secondary to adverse effects.

A randomized, multicenter, double-blind, parallel-group study compared the efficacy of lansoprazole with omeprazole in duodenal ulcer healing and prevention of relapse.[89] A total of 251 patients with duodenal ulcer were treated with either lansoprazole 30 mg (n=167) or omeprazole 40 mg (n=84) daily. Patients with healed ulcers were then randomly allocated to 12 months of maintenance therapy with lansoprazole 15 mg (n=74), lansoprazole 30 mg (n=71), or omeprazole 20 mg (n=73) daily. Healing rates at four weeks were 93.9 percent with lansoprazole and 97.5 percent with omeprazole, with no significant differences between groups. Endoscopic relapse rates after six months were 4.5 percent with lansoprazole 15 mg, zero percent with lansoprazole 30 mg, and 6.3 percent with omeprazole 20 mg, compared with 3.3 percent, zero percent, and 3.5 percent, respectively, at 12 months. There were no significant differences among groups. The incidence of adverse events during acute treatment was six percent and 7.1 percent in the lansoprazole and omeprazole groups, respectively. During maintenance therapy, adverse events occurred in 12.2 percent of patients treated with lansoprazole 15 mg, 5.6 percent with lansoprazole 30 mg, and 11 percent with omeprazole 20 mg.

<u>rabeprazole (Aciphex) versus omeprazole (Prilosec)</u>

A randomized, double-blind, multicenter study compared the efficacy and tolerability of rabeprazole and omeprazole in patients with active duodenal ulcers.[90] Patients with active duodenal ulcer received rabeprazole 20 mg (n=102) or omeprazole 20 mg (n=103) once daily for two or four weeks with ulcer healing monitored by endoscopy. After two weeks, complete ulcer healing after two weeks was documented in 69 percent of patients given rabeprazole and in 62 percent of patients given omeprazole (p=0.083). After four weeks, healing rates were 98 percent in the rabeprazole group and 93 percent in the omeprazole group (p=NS). Rabeprazole-treated patients had significantly greater improvement in daytime pain symptom relief than those treated with omeprazole at the conclusion of the study (p=0.038). Both drugs were well tolerated over the four-week treatment period. The study concluded that rabeprazole produced healing rates equivalent to omeprazole at weeks two and four.

Erosive Esophagitis

The Los Angeles (LA) classification is typically used to grade the severity of esophagitis. Grade A indicates that there are one or more isolated mucosal breaks less than or equal to five millimeters long.[91] Grade B esophagitis has one or more isolated mucosal breaks greater than five millimeters in length. Grade C involves one or more mucosal breaks bridging the tops of folds in the esophagus but involving less than 75 percent of the circumference. Grade D esophagitis is one or more mucosal breaks bridging the tops of folds and involving greater than 75 percent of the esophageal circumference.

<u>esomeprazole (Nexium) versus lansoprazole (Prevacid)</u>

A multicenter, randomized, double-blind, parallel-group trial compared esomeprazole with lansoprazole for healing of erosive esophagitis and resolution of heartburn.[92] The trial enrolled 5,241 adult patients with endoscopically documented erosive esophagitis, graded by severity at baseline. Patients received 40 mg of esomeprazole (n=2,624) or 30 mg of lansoprazole (n=2,617) once daily before breakfast for up to eight weeks. The primary efficacy endpoint was healing of erosive esophagitis at week eight. Secondary assessments included proportion of

patients healed at week four, resolution of investigator-recorded heartburn, time to first resolution and time to sustained resolution of patient diary-recorded heartburn, and proportion of heartburn-free days and nights. Esomeprazole 40 mg demonstrated significantly higher healing rates (92.6 percent) than lansoprazole 30 mg (88.8 percent) at week eight (95% CI, 7.5–90.0 percent; p=0.0001). A significant difference in healing rates favoring esomeprazole was also observed at week four. The difference in healing rates between esomeprazole and lansoprazole increased as baseline severity of erosive esophagitis increased. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole. Sustained resolution of nocturnal heartburn also occurred faster with esomeprazole. Both treatments were well tolerated. Esomeprazole 40 mg is at least as effective as lansoprazole 30 mg in healing erosive esophagitis and resolving heartburn. Healing rates are consistently high with esomeprazole regardless of baseline disease severity.

To compare healing rates with esomeprazole versus lansoprazole in patients with moderate to severe erosive esophagitis, a multicenter, randomized, double-blind, parallel-group trial enrolled 999 patients with endoscopically confirmed moderate or severe erosive esophagitis.[93] Patients received esomeprazole 40 mg (n=498) or lansoprazole 30 mg (n=501) once daily for up to eight weeks. The primary end point was erosive esophagitis healing through week eight. Secondary assessments included investigator-assessed resolution of symptoms and safety and tolerability. Estimated healing rates at week eight were 82.4 percent with esomeprazole and 77.5 percent with lansoprazole. Heartburn resolved at week four in 72 percent and 64 percent of patients who received esomeprazole and lansoprazole, respectively (p=0.005). Control of other GERD symptoms was similar between treatments groups, and both treatments were well tolerated.

A double-blind, randomized, parallel-group, multicenter, maintenance trial enrolled patients (n=1,026) previously treated for erosive esophagitis with no endoscopic evidence of ongoing disease and who were symptom-free (no heartburn or acid regurgitation symptoms) during the week prior to initiating maintenance therapy.[94] Patients with Los Angeles grades C and D erosive esophagitis at baseline were randomized to treatment with either esomeprazole 40 mg or lansoprazole 30 mg once daily. Patients with Los Angeles grades A and B erosive esophagitis at baseline received esomeprazole 40 mg. Following initial treatment, patients were randomized to maintenance once-daily therapy with esomeprazole 20 mg or lansoprazole 15 mg for up to six months. Esophago-gastroduodenoscopies were completed at months three and six, and investigators assessed symptom severity at months one, three, and six. Estimated endoscopic/symptomatic remission rate during a period of six months was significantly higher (p=0.0007) for patients who received esomeprazole 20 mg once daily (84.8 percent) compared with those who received lansoprazole 15 mg (75.9 percent). There were no significant differences between treatments for reflux symptoms. Both treatments were well tolerated.

<u>esomeprazole (Nexium) versus omeprazole (Prilosec)</u>

The study was designed to evaluate the efficacy and tolerability of esomeprazole relative to omeprazole in healing erosive esophagitis and resolving accompanying symptoms of GERD.[95] Esomeprazole 40 mg once daily was compared with omeprazole 20 mg once daily in 2,425 patients with erosive esophagitis (*H. pylori*-negative by serology) in an eight-week, multicenter, randomized, double-blind, parallel-group study. The primary efficacy endpoint was the proportion of patients with healed esophagitis at eight weeks. Secondary endpoints were the proportion of patients healed at week four, resolution of heartburn at week four, time to first resolution and sustained resolution of heartburn, and proportion of heartburn-free days and nights. Significantly more patients were healed with esomeprazole versus omeprazole at week eight (93.7 percent versus 84.2 percent, respectively; p<0.001). Healing rates at week four

were 81.7 percent and 68.7 percent, respectively. Secondary outcome measures favored esomeprazole. Tolerability and safety of esomeprazole are comparable to omeprazole.

To compare esomeprazole with omeprazole for healing erosive esophagitis, 1,148 patients with endoscopically confirmed erosive esophagitis were randomized to daily esomeprazole 40 mg or omeprazole 20 mg for eight weeks in a multicenter, double-blind, parallel-group trial.[96] The primary outcome was the proportion of patients with healed erosive esophagitis at week eight. At week eight, estimated healing rates were 92.2 percent (95% CI, 89.9-94.5 percent) with esomeprazole and 89.8 percent (95% CI, 87.2-92.4 percent) with omeprazole. The treatments showed comparable tolerability profiles.

A similarly designed, multicenter, double-blind, parallel-group eight-week study compared low-dose esomeprazole 20 mg daily with omeprazole 20 mg daily in 1,176 patients with confirmed erosive esophagitis (*H. pylori*-negative by serology) and found no significant difference in healing rates.[97] The primary outcome of the study was the proportion of patients with healed EE through week eight. Secondary outcomes included diary and investigator assessments of heartburn symptoms. Cumulative life-table healing rates at week eight were similarly high for esomeprazole 20 mg (90.6 percent; 95% CI, 88.1-93) and omeprazole 20 mg (88.3 percent; 95% CI, 85.5-91.0). Both treatments were comparable for other secondary measures and had similar tolerability profiles.

Esomeprazole 20 mg and 40 mg and omeprazole 20 mg, each given once daily, were evaluated in the healing and symptom resolution of endoscopically confirmed reflux esophagitis in 1,960 patients in a randomized, double-blinded trial.[98] The primary efficacy variable was the proportion of patients healed at week eight. Secondary variables included healing and heartburn resolution at week four, time to first resolution and sustained resolution of heartburn, and percent of heartburn-free days and nights. Significantly more patients were healed at week eight with esomeprazole 40 mg (94.1 percent) and 20 mg (89.9 percent) compared to omeprazole 20 mg (86.9 percent) (each $p<0.05$). Esomeprazole 40 mg was also significantly more effective than omeprazole for healing at week four and for all secondary variables evaluating heartburn resolution. Tolerability was similar in all groups.

esomeprazole (Nexium) versus pantoprazole (Protonix)

In the eight-week EXPO study, the efficacy of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive esophagitis in 3,151 patients with a history of symptomatic GERD (six months or more) and heartburn on at least four of the seven days preceding enrollment was examined.[99] Endoscopies were performed to grade erosive esophagitis severity using the Los Angeles (LA) classification system at baseline, four weeks, and eight weeks (if unhealed at four weeks). Heartburn severity was recorded by patients on diary cards. The primary end point was healing of erosive esophagitis by week eight of treatment. Esomeprazole 40 mg healed a significantly greater proportion of erosive esophagitis patients than pantoprazole 40 mg at both four weeks (esomeprazole 81 percent, pantoprazole 75 percent, $p<0.001$) and eight weeks (esomeprazole 96 percent, pantoprazole 92 percent, $p<0.001$). The median time to reach sustained heartburn resolution was six days in patients receiving esomeprazole and eight days with pantoprazole ($p<0.001$).

In the six-month maintenance phase of the EXPO study, patients (n=2,766) with symptoms of GERD and endoscopically confirmed erosive esophagitis at baseline were randomized to treatment with either esomeprazole 20 mg or pantoprazole 20 mg for up to eight weeks.[100] The study was double-blinded. Patients free of moderate/severe heartburn and acid regurgitation and with healed erosive esophagitis at four to eight weeks continued the assigned treatment

regimen into a six-month maintenance therapy phase of the study. Following six months of treatment, the proportion of patients with endoscopic and symptomatic remission was significantly greater for those receiving esomeprazole 20 mg than pantoprazole 20 mg (87 versus 74.9 percent; p<0.0001). Esomeprazole produced a higher proportion of patients free of moderate/severe GERD symptoms and fewer discontinuations due to ongoing symptoms than pantoprazole (92.2 versus 88.5 percent, respectively; p<0.001).

dexlansoprazole (Dexilant) versus lansoprazole (Prevacid)

In two multicenter, double-blind, active-controlled, randomized, eight-week studies, 4,092 patients with endoscopically confirmed erosive esophagitis (EE) were randomized to one of the following three treatment groups: dexlansoprazole 60 mg daily, dexlansoprazole 90 mg daily, or lansoprazole 30 mg daily.[101] Based on the Los Angeles Classification Grading System (Grades A-D), 71 percent of patients had mild EE (Grades A and B) and 29 percent of patients had moderate to severe EE (Grades C and D) before treatment. The studies were designed to test non-inferiority. In Studies 1 and 2, 70 and 66 percent of patients, respectively, that received dexlansoprazole 60 mg experienced healing at week four, compared to 65 percent of patients, in both studies who received lansoprazole. At week eight, 87 and 85 percent of patients in studies 1 and 2, respectively, that received dexlansoprazole 60 mg experienced healing, compared to 85 and 79 percent of patients receiving lansoprazole. Non-inferiority was demonstrated in both studies. Dexlansoprazole 90 mg did not provide additional clinical benefit over dexlansoprazole 60 mg.

Gastric Ulcer

rabeprazole (Aciphex) versus omeprazole (Prilosec)

A randomized, double-blind, multicenter study compared rabeprazole and omeprazole in patients with active gastric ulcers.[102] Two hundred twenty-seven patients were randomized to receive either rabeprazole 20 mg (n=113) or omeprazole 20 mg (n=114) once daily for three or six weeks, with healing monitored by endoscopy. After three weeks, complete healing was documented in 58 percent of rabeprazole patients and 61 percent of omeprazole patients (p=NS). After six weeks, healing rates were identical in both groups at 91 percent. Differences in symptom relief significantly favored rabeprazole at week three for daytime pain improvement (p=0.023), at week six for pain frequency (p=0.006), and complete resolution of night pain (p=0.022). Both drugs were well-tolerated over the six-week treatment course.

pantoprazole (Protonix) versus omeprazole (Prilosec)

A randomized, double-blind study in 219 patients with benign gastric ulcers compared pantoprazole 40 mg (n=146) and omeprazole 20 mg (n=73) once daily.[103] Treatment was administered for four weeks and extended another four weeks if the ulcer had not healed. After four weeks, complete ulcer healing was seen in 88 percent of pantoprazole patients and 77 percent of patients treated with omeprazole (p<0.05). At eight weeks, the corresponding values were 97 percent and 96 percent, respectively (p=NS). Ten percent of patients in each group reported adverse events.

GERD

The Savary-Miller classification is used to grade the severity of GERD. Grade I GERD has one or more erosions in one mucosal fold of the esophagus. Grade II has one or more erosions in several mucosal folds (erosions may merge). In Grade III GERD, erosions surround the

circumference of the esophagus. Ulcers, strictures, and/or esophageal shortening occur in Grade IV. Grade V is known as Barrett's Esophagus and involves intestinal metaplasia, where the morphology of the esophageal lining is transformed to resemble intestinal mucosa.

lansoprazole (Prevacid) versus omeprazole (Prilosec)

A double-blind, randomized clinical trial comparing 20 mg omeprazole and 30 mg lansoprazole, given daily, evaluated efficacy in 229 patients with reflux esophagitis.[104] The treatment period was four or eight weeks, and main efficacy outcomes were healing of endoscopic changes, relief of reflux symptoms, and occurrence of adverse events. No significant difference in terms of healing was found, either after four or eight weeks of treatment. Patients receiving lansoprazole experienced a greater improvement in heartburn after four weeks ($p=0.03$), and there was a similar trend for acid regurgitation.

In a double-blind, multicenter study, 1,284 patients with endoscopically diagnosed erosive reflux esophagitis were randomized to received lansoprazole 15 or 30 mg, omeprazole 20 mg, or placebo once daily for eight weeks.[105] Healing was evaluated endoscopically. Healing rates at two, four, six, and eight weeks were 65.3, 83.3, 89.4, and 90 percent, respectively, for lansoprazole 30 mg; 56.3, 74.6, 80.3, and 78.8 percent for lansoprazole 15 mg; 60.9, 82, 89.7, and 90.7 percent for omeprazole 20 mg; and 23.9, 32.8, 36.6, and 40 percent for placebo. Healing rates for lansoprazole 30 mg were significantly higher than lansoprazole 15 mg at all time points ($p<0.05$). Healing rates for omeprazole 20 mg were significantly higher than with lansoprazole 15 mg at four, six, and eight weeks, and were similar to those with lansoprazole 30 mg. Based on patient diaries, lansoprazole 30 mg produced better symptomatic relief than lansoprazole 15 mg or omeprazole 20 mg, primarily early in the treatment course.

A double-blind, randomized, multicenter study compared the efficacy and safety of lansoprazole 30 mg and omeprazole 40 mg daily in the treatment of moderate (Savary-Miller grade II) as well as severe (Savary-Miller grade III/IVa) reflux esophagitis.[106] The trial enrolled 211 patients. Healing was assessed by endoscopy after four weeks and, if necessary, eight weeks. Symptom relief was determined by symptom assessments at the same time points. There were no significant differences in healing after four weeks (87.5 percent for lansoprazole, 80.6 percent for omeprazole; 95% CI, -4.0; +17.8) or overall healing (96.1 percent for lansoprazole, 93.1 percent for omeprazole; 95% CI, -4.2; +10.2) between the two groups. Relief of reflux-related symptoms at four and eight weeks did not differ significantly between the treatment groups. No difference in the incidence of adverse events was observed between the groups.

lansoprazole (Prevacid) versus pantoprazole (Protonix)

The efficacy of pantoprazole 40 mg or lansoprazole 30 mg daily on endoscopic healing and symptom relief in Savary-Miller grade II-III reflux esophagitis patients was compared after four and eight weeks of administration.[107] Four-hundred sixty-one patients were included in the prospective, randomized, multicenter double-blind study. The difference in healing rates at four and eight weeks were not statistically significant. Healing rates at four weeks were 81 and 80 percent in the pantoprazole and lansoprazole groups, respectively, and 90 and 86 percent at eight weeks, respectively. The heartburn relief rates at day 14 were 88 percent and 86 percent in the pantoprazole and lansoprazole groups, respectively.

pantoprazole (Protonix) versus esomeprazole (Nexium)

In a multicenter, randomized, double-blind study, 227 patients with GERD grades B or C (Los Angeles classification) received 40 mg pantoprazole or 40 mg esomeprazole daily.[108]

Endoscopically verified healing was assessed at the first and final visit (after four, six, eight, or 10 weeks of treatment). Overall healing in the treatment groups was 95 percent (pantoprazole) and 90 percent (esomeprazole); rates were not statistically significantly different. Pantoprazole and esomeprazole demonstrated comparable safety and tolerability.

The efficacy of pantoprazole 20 mg and esomeprazole 20 mg on-demand for long-term management of patients with mild GERD (Los Angeles classification grades A or B) was evaluated in a biphasic clinical trial.[109] During the acute phase (initial 28 days), 236 patients received pantoprazole 20 mg once daily. Patients without heartburn (n=199) during the final three days of the acute phase were eligible to enter the long-term phase of six months on-demand treatment with esomeprazole. Antacids were provided as rescue medication during this phase. Based on patient diary, the mean intensity of heartburn symptoms was significantly lower for on-demand pantoprazole (p=0.012). Mean symptom intensities of acid eructation and pain on swallowing, both separately and as a combined symptom score, and mean duration of the symptoms during on-demand treatment, were compared between the two treatment groups. The combined symptom score of the three symptoms heartburn, acid eructation, and pain on swallowing was numerically lower in the pantoprazole group compared with the esomeprazole group (1.72 versus 1.99, respectively). Tablet intake was comparable in both groups. Pantoprazole 20 mg and esomeprazole 20 mg on-demand are comparable and effective treatment strategies for the long-term treatment of non-erosive and mild GERD.

pantoprazole (Protonix) versus omeprazole (Prilosec)

To compare pantoprazole 40 mg once daily with omeprazole 20 mg once daily in the treatment of reflux esophagitis (grades II and III), a double-blind, randomized, multicenter study evaluated 286 patients.[110] Patients underwent endoscopy upon study entrance and again after four weeks, and continued to receive an additional four weeks of treatment if esophagitis was not resolved. After four weeks of treatment, complete healing occurred in 74 percent of patients in the pantoprazole group and 78 percent patients in the omeprazole group. At eight weeks, the respective healing rates were 90 percent and 94 percent. Differences between the treatment groups were not significant. Improvement in the principal symptoms of reflux esophagitis was also similar between the treatment groups. Fifty-nine percent of patients treated with pantoprazole and 69 percent of patients treated with omeprazole showed improvement at two weeks and 83 percent and 86 percent, respectively, at four weeks, were free from symptoms. Both treatments were well tolerated.

rabeprazole (Aciphex) versus omeprazole (Prilosec)

In a randomized, double-blind, multicenter study, the efficacy and safety of rabeprazole and omeprazole were compared in patients with erosive or ulcerative GERD.[111] Patients received rabeprazole 20 mg once daily (n=100) or omeprazole 20 mg (n=102) once daily for four or eight weeks, with healing verified by endoscopy. GERD healing rates evaluated at weeks four and eight were equivalent. Four-week healing rates for rabeprazole and omeprazole were 81 percent and 81 percent, respectively, and 92 percent and 94 percent, respectively, at eight weeks. Both drugs were well tolerated over the eight-week treatment period.

The efficacy and tolerability of rabeprazole and omeprazole in preventing relapse of healed erosive GERD was evaluated in a multicenter, double-blind, parallel-group study conducted in 243 patients.[112] Patients were randomized to receive rabeprazole 10 or 20 mg or omeprazole 20 mg once daily. Endoscopy was performed at weeks 13, 26, 39, and 52, or when symptoms suggested recurrence. Rabeprazole 10 mg and 20 mg were equivalent to omeprazole 20 mg for all outcome parameters. At week 52, relapse rates in the intent-to-treat population were five

percent, four percent, and five percent for rabeprazole 10 mg and 20 mg and omeprazole 20 mg, respectively. All treatments were well tolerated.

A study of patients' preferences showed patients were equally satisfied with two of the PPIs, and most patients would be willing to switch drugs within the class. A double-blind, double-dummy, crossover trial randomized 240 patients to receive daily treatment for four weeks each with omeprazole 20 mg and rabeprazole 20 mg.[113] At the end of eight weeks, patients compared the two medications using seven criteria. Results showed the majority of patients could be switched to another PPI, predictably without noticeable difference in ongoing primary symptom control. Based on the variables assessed, approximately one-third to one-half of patients were able to express a preference for one of the treatments. For "absence of unwanted side effects" and "presence of positive side effects", a statistically significant difference in favor of rabeprazole was detected (p=0.0467 and p=0.0188, respectively). In the primary outcome variable, total treatment preference score, however, no statistically significant difference between the two PPIs was detected (p=0.0754). There was no difference in tolerability between rabeprazole and omeprazole, with slightly more than one-half of patients in each group reporting at least one adverse event. Patients indicated the most important drug characteristics for treating this condition were rapid and lasting control of pain. Most (83.6 percent) patients already controlled on a PPI indicated they would be willing to try an alternative medication within the drug class.

H. pylori eradication

rabeprazole (Aciphex) versus omeprazole (Prilosec)

In a prospective, controlled, double-blind trial, 803 patients with confirmed *H. pylori* presence were randomized to receive rabeprazole 20 mg twice daily for three, seven, or ten days or omeprazole 20 mg twice daily for ten days.[114] In addition, all patients received concurrent amoxicillin 1 gm and clarithromycin 500 mg twice daily. *H. pylori* eradication rates were significantly lower for the three-day rabeprazole regimen (27 percent) than in the seven (77 percent) or ten day (78 percent) courses of rabeprazole or the ten-day course of omeprazole (73 percent). There was no significant difference between the seven or ten day courses of treatment.

A double-blind, randomized study was designed to determine whether rabeprazole- and omeprazole-based triple therapy regimens are therapeutically equivalent in the eradication of *H. pylori*.[115] Three hundred forty-five patients with current or previously active peptic ulcer and a positive *H. pylori* urease test were randomly assigned to receive rabeprazole 20 mg or omeprazole 20 mg with either amoxicillin 1 gm or metronidazole 400 mg twice daily. In addition, all patients received clarithromycin 500 mg twice daily. Eradication rates were 77 and 75 percent with rabeprazole and omeprazole, respectively (p=NS). In patients receiving amoxicillin and clarithromycin, rabeprazole produced a higher, but not statistically significant, eradication rate than omeprazole (94 versus 84 percent). In patients receiving clarithromycin and metronidazole, rabeprazole produced a lower, but not statistically significant, eradication rate than omeprazole (79 versus 86 percent). Ulcer healing rates were higher than 90 percent with *H. pylori* eradication. All regimens were well tolerated.

Summary

There are differences among the PPIs in FDA-approved indications and dosage forms.

Lansoprazole (Prevacid) has a unique indication for long-term maintenance therapy of healed

duodenal ulcers. Esomeprazole (Nexium) and lansoprazole (Prevacid) are indicated for the reduction of risk of NSAID-associated gastric ulcers. Most PPIs are indicated for GERD or GERD-related management with the exception of the OTC formulations. Esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprazole (Aciphex) are indicated for short-term management of esophagitis and/or GERD in children. Omeprazole (Prilosec), lansoprazole (Prevacid), esomeprazole (Nexium), omeprazole/sodium bicarbonate (Zegerid), and pantoprazole (Protonix) are available as formulations intended for use as suspensions.

Except for dexlansoprazole (Dexilant), pantoprazole (Protonix), omeprazole/sodium bicarbonate (Zegerid), and omeprazole OTC (Prilosec OTC), each of the PPIs is indicated, in combination with clarithromycin and/or amoxicillin, for eradication of *H. pylori.* Rabeprazole (Aciphex) is indicated for a seven-day course of treatment while esomeprazole (Nexium), lansoprazole (Prevacid), and omeprazole (Prilosec) require 10 to 14 days of treatment.

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