Proton Pump Inhibitors
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS (ADULTS)[1,2,3,4,5,6,7,8,9]

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	X	--	--	--
esomeprazole magnesium (Nexium®; Esomep-EZS™)	generic, Astra Zeneca, Puretek	--	--	--	X with amoxicillin + clarithromycin	X	X	X	X	--	X (risk reduction)
esomeprazole magnesium OTC (Nexium® 24HR)	generic, Pfizer	--	--	X	--	--	--	--	--	--	--
esomeprazole strontium	Hanmi	--	--	--	X with amoxicillin + clarithromycin	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	--	--	--	--	--	--	--

FDA-Approved Indications (Adults) (continued)

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			
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®)	generic, Eisai	X	--	--	X with amoxicillin + clarithromycin	X (adults and pediatrics)	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 magnesium (Nexium) is indicated for the short-term treatment of GERD in children one to 17 years old.
- Esomeprazole magnesium (Nexium 24HR) is available over-the-counter (OTC) in 20 mg strength and is only FDA approved for use in adults for the treatment of frequent heartburn (two or more days a week). The Indicated course of therapy is 14 days. Esomeprazole magnesium 20 mg and 40 mg (Nexium) is available with a prescription for its currently approved indications
- Esomeprazole strontium is indicated for the short-term treatment of GERD. Safety and efficacy has not been established in pediatric patients

- 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, maintenance of healing of EE and treatment of EE in children one to 16 years and the short-term treatment of EE in patients aged 1 month to less than 1 year of age.
- Rabeprazole (Aciphex) is indicated for the short-term treatment of symptomatic GERD in children 12 years of age and older and for the treatment of GERD in pediatric patients 1 to 11 years old.
- Pantoprazole (Protonix) is indicated for short-term treatment of erosive esophagitis associated with GERD in children ages five years and older.
- *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.
- Dexlansoprazole (Dexilant) is indicated for the healing of EE, maintenance of healing of EE and treatment of heartburn, and treatment of non-erosive GERD in children 12 years of age and older.
- Fixed-dose delayed-release tablets of aspirin and omeprazole (Yosprala™) are indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers.[10] Yosprala™ is not included in this Therapeutic Class Review.
- Omeprazole is available over-the-counter (OTC) in 20 mg extended-release orally disintegrating tablets and is only FDA-approved for use in adults for the treatment of frequent heartburn (≥ 2 days a week). The indicated course of therapy is 14 days. Omeprazole (Prilosec) is available with a prescription for its currently approved indications.

Esomeprazole/naproxen (Vimovo®) by AstraZeneca is indicated for patients requiring naproxen for symptomatic relief of arthritis and esomeprazole magnesium to decrease the risk of developing naproxen-associated gastric ulcers. Its use is not addressed in this class review.

OVERVIEW

Proton pump inhibitors (PPIs) demonstrate gastric acid suppression superior to histamine-2 receptor antagonists (H2RAs). PPIs achieve a more rapid and sustained increase in gastric pH and are not associated with the rapid tachyphylaxis seen with H2RAs, 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.

Acid suppression is the mainstay of therapy for GERD. The American Gastroenterological Association (AGA) and the American College of Gastroenterology (ACG) recommend PPIs as first-line therapy for the treatment of severe GERD-related symptoms or erosive esophagitis (EE).[11,12] H2RAs can be used in patients with mild symptoms or verified nonerosive disease. PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients.

The AGA also states that for healing esophagitis and symptomatic relief, PPIs are more effective than H2RAs, and H2RAs are more effective than placebo.[13] 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 and diagnostic testing may be warranted. Patients with suspected reflux chest pain syndrome (after a cardiac etiology has been carefully evaluated) may be given a 4-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 after initial response to PPI therapy. 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 H2RAs or PPIs accelerates ulcer healing and provides rapid symptomatic improvement.

NSAID use, the second-most common cause of PUD, is largely responsible for an epidemic of upper gastrointestinal (GI) bleeding and perforation in the elderly. Continued NSAID use may delay healing of ulcers.[14] PPIs are as effective as misoprostol at reducing NSAID-induced ulcer formation and are better tolerated.[15,16]

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.[17] 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 H2RAs do not prevent most NSAID-related gastric ulcers, 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.[18,19] The guidelines state that PPIs are more effective than H2RAs in healing esophagitis, symptomatic relief, and maintaining healing of esophagitis. The 2015 ACG guidelines on Barrett's esophagus recommend once daily PPI therapy and recommend against routine use of twice daily regimens unless needed for poor control of reflux symptoms or esophagitis.[20] A further review, conducted by the AGA in 2017, updated the guidelines to specify that long-term use of PPIs for the treatment of patients with symptomatic GERD and Barrett's esophagus is recommended and that consideration of long-term PPI treatment for patients with asymptomatic Barrett's esophagus be made as long as the dose is periodically reevaluated so that the lowest effective dose is used based on symptom control. Additionally, long-term PPI users should not routinely use probiotics to prevent infection, raise their intake of calcium, vitamin B12, or magnesium beyond the Recommended Daily Allowance (RDA), and should not be routinely screened or monitored for bone mineral density, serum creatinine, magnesium, or vitamin B12.[21]

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.[22] A short course of PPI therapy has demonstrated better symptom control than therapy with H2RAs 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%, 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 4 to 8 weeks. Long-term empiric antisecretory therapy may lead to inappropriate maintenance therapy that the patient does not require and 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. In 2017, the guidelines were updated to suggest that patients ≥ 60 years of age or with higher risk of malignancy and presenting with dyspepsia should be investigated with an upper gastrointestinal endoscopy to exclude organic pathology and further define the patient as having functional dyspepsia (FD) when no pathology is found. These patients should also be offered *H. pylori* testing and eradication if an infection is found or PPI, tricyclic antidepressant (TCA), and prokinetic therapy (in that order) for *H. pylori*-negative or cases of treatment failure. Alarm features should not automatically result in an endoscopy in younger patients and endoscopy should be considered on a case by case basis. For patients < 60 years of age, *H. pylori* testing is recommended with treatment indicated for positive cases and empiric PPI therapy given if the patient is determined to be negative or not responding to the initial treatment. If PPI therapy is ineffective, TCAs or prokinetic therapies can be tried.[23]

The 2013 ACG 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 H2RAs.[24] Empiric medical therapy with a PPI is recommended with a presumptive

diagnosis of GERD based on symptoms of heartburn and regurgitation. Patients with non-cardiac chest pain suspected due to GERD should have diagnostic evaluation before institution of therapy. PPI therapy should be initiated at once a day dosing, before the first meal of the day. Traditional delayed-release PPIs should be administered 30 to 60 minutes before a meal for maximal pH control, while newer PPIs, such as dexlansoprazole (Dexilant) and omeprazole-sodium bicarbonate (Zegerid), may offer dosing flexibility relative to meal timing. In patients with partial response to PPI therapy, increasing the dose to a twice daily therapy or switching to a different PPI may provide additional symptom relief. In addition, adjustment of dose timing may be considered in patients with night-time symptoms, variable schedules, and/or sleep disturbance. Patients who respond to short-term PPIs should subsequently attempt to stop or reduce the dose of the PPI, and those who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (e.g., central obesity, large hiatal hernia). PPIs should be administered in the lowest effective dose, including on-demand or intermittent therapy for those who require long-term therapy. Risk factors for lack of symptom control have included patients with longer duration of disease, presence of hiatal hernia, extraesophageal symptoms, and lack of compliance.

The International Consensus Recommendations on the Management of Patients with Nonvariceal Upper GI Bleeding were updated in 2019 and recommend that high risk patients with bleeding ulcers with successful endoscopic treatment receive high-dose PPI therapy (intravenous loading dose, then continuous infusion) for 3 days.[25] This should then be followed by an oral PPI twice daily through day 14, followed by once daily treatment for a total duration dependent on the severity of the bleeding lesion. PPI therapy is suggested as secondary prophylaxis for patients with previous ulcer bleeding who are receiving antiplatelet or anticoagulant therapy.

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.[26,27,28]

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 sulfonamide moiety that binds to the luminal surface of H+/K+-ATPase, thereby irreversibly inhibiting the gastric proton pump.[29,30] A profound, long-lasting antisecretory effect is produced, capable of maintaining the gastric pH above 4, even during postprandial acid surges.[31]

PHARMACOKINETICS[32,33,34,35,36,37,38,39]

Drug	Bioavailability (%)	$t_{1/2}$ (hours)	T_{max} (hours)	Metabolism	Elimination (%)
dexlansoprazole (Dexilant)	47-60	1-2	1-2 then 4-5	Hepatic by CYP 3A4, 2C19 to inactive metabolites Metabolism of active drug is nearly 100%	Urine: 50.7 Feces: 47.6
esomeprazole magnesium (Nexium, Nexium 24HR)	64-90	1.0-1.5	1.5		Urine: 80 Feces: 20
esomeprazole strontium	Similar to esomeprazole magnesium delayed-release	1.0-1.5	1.7		Urine: 80 Feces: 20
lansoprazole (Prevacid)	80	< 2	1.7		Urine: 33 Feces: 67
omeprazole (Prilosec)	30-40	0.5-1	0.5-3.5		Urine: 77 Feces: 23
omeprazole/ sodium bicarbonate (Zegerid)	30-40	1	0.5		Urine: 77 Feces: 23
pantoprazole (Protonix)	77	1	2.5		Urine: 71 Feces: 18
rabeprazole (Aciphex)	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.[40] Although PPIs have short plasma elimination half-lives, duration of gastric acid inhibition is prolonged due to irreversible binding to the proton pump.[41] With continued daily dosing, bioavailability increases for esomeprazole and omeprazole.

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.[42] 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.[43]

Each esomeprazole strontium delayed-release capsule contains 24.65 mg esomeprazole strontium equivalent to 20 mg esomeprazole or 49.3 mg esomeprazole strontium equivalent to 40 mg esomeprazole. Mean esomeprazole maximum plasma concentration (Cmax) and area under the

plasma concentration-time curve (AUC) were comparable to those for esomeprazole magnesium delayed-release capsules 44.6 mg (equivalent to 40 mg of esomeprazole).

CONTRAINDICATIONS/WARNINGS[44,45,46,47,48,49,50,51,52]

PPIs are contraindicated in patients with known hypersensitivity to any component of the formulation. Reactions of angioedema, anaphylaxis, bronchospasms, urticaria, and acute interstitial nephritis have been observed. Acute interstitial nephritis may occur at any point during therapy with a PPI and should result in discontinuation of the PPI therapy.

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 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). According to ACG, patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture.[53] 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 (for at least 3 months and in most cases, longer than 1 year).[54] Low serum magnesium levels can result in serious adverse events including tetany, arrhythmias, and 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.

The use of PPIs may be associated with an increased chance of developing *Clostridium difficile*-associated diarrhea (CDAD). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated and should seek immediate medical attention for severe diarrhea that does not improve. It should be noted that geriatric patients, patients on a concurrent

broad spectrum antibiotic and patients with other chronic disease states are at a higher risk for developing PPI related CDAD.

Increases in intragastric pH, caused by omeprazole or esomeprazole therapy, may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A (CgA) levels. This may interfere with diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily discontinue esomeprazole or omeprazole treatment no less than 14 days before assessing CgA levels. If initial CgA levels are high, consideration should be given to repeating the test and the same commercial laboratory should be used for testing.

In rare cases, long-term (e.g. longer than 3 years) daily use of acid-suppressing medications have been shown to cause malabsorption of cyanocobalamin (vitamin B-12) caused by hypochlorhydria. Healthcare providers should consider a diagnosis of vitamin B-12 deficiency if clinical symptoms are observed in patients.

False positives in tetrahydrocannabinol (THC) urine screening tests have been reported in patients receiving PPIs. Alternative confirmatory methods should be used to verify positive results.

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs.[55] The majority of the cases of PPI-induced lupus were CLE and were seen in patients ranging in age from infants to the elderly. The cases have occurred as both new onset and an exacerbation of existing autoimmune disorders and consist of positive antinuclear antibodies (ANA) and histologic findings without organ involvement. When signs or symptoms of SLE or CLE occur, the PPI therapy should be discontinued and patients referred to the appropriate specialist for evaluation. Complete recovery is generally attained within 4 to 12 weeks after discontinuation of PPI therapy. It is recommended to avoid administration of PPIs for longer than medically indicated.

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond 1 year. Most patients with fundic gland polyps were asymptomatic. PPIs should be used for the shortest duration appropriate for the condition being treated.

Discontinue esomeprazole and omeprazole and contact a physician if rash or joint pain occur.

DRUG INTERACTIONS[56,57,58,59,60,61,62,63]

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) and esomeprazole (Nexium, Nexium 24HR, esomeprazole strontium) inhibit CYP2C19, potentially leading to interactions with diazepam and phenytoin.

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 (Reyataz®) and nelfinavir (Viracept®), HIV protease inhibitors, rilpivirine-containing products, and erlotinib (Tarceva®) require the presence of gastric acid for absorption; therefore, PPIs reduce gastric acid and systemic absorption of these medications and 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 esomeprazole, 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 esomeprazole 40 mg (Nexium) or omeprazole 80 mg (even when administered 12 hours apart) reduces the pharmacological activity of clopidogrel. The FDA states that there is no evidence that other H2RAs 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). In 2014, the FDA labeling was updated again to suggest that PPI use in patients taking clopidogrel be limited to pantoprazole, rabeprazole, lansoprazole, and dexlansoprazole.[64]

A crossover clinical study, 66 healthy participants were given clopidogrel, 300 mg loading dose followed by 75 mg daily, alone or with pantoprazole 80 mg, for 5 days.[65] The agents were given at the same time. On day 5 the mean area under the curve (AUC) of the active metabolite of clopidogrel was reduced by 14% when coadministered with pantoprazole compared to clopidogrel given alone. Pharmacodynamic parameter measurements demonstrated a change in platelet inhibition correlating to the change in AUC. The clinical significance of this finding is unclear.

A randomized, open-label, 2-period, crossover study showed that the AUC of the active metabolite of clopidogrel was reduced by approximately 9% when dexlansoprazole was coadministered with clopidogrel compared to administration of clopidogrel alone.[66] No dosage adjustment is required when the 2 agents are administered concurrently.

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 2 types of drugs.[67] 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. PPIs are not recommended to reduce upper GI bleeding in patients who have a low risk of upper GI bleeding, and who have much less potential to benefit from prophylactic therapy.

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.

Concomitant use of PPIs with methotrexate (primarily at high doses) may elevate and prolong serum levels of methotrexate and/or its metabolite and may lead to methotrexate toxicities. Consider temporary withdrawal of PPI therapy in patients receiving high-dose methotrexate.

Voriconazole (Vfend®), a combined inhibitor of CYP2C19 and CYP3A4, may lead to a 2-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.

Avoid concomitant use of esomeprazole or omeprazole with St. John's wort or rifampin due to the potential reduction in esomeprazole or omeprazole levels, respectively.

ADVERSE EFFECTS[68,69,70,71,72,73,74,75]

Drug	Abdominal Pain	Diarrhea	Headache	Nausea
dexlansoprazole (Dexilant)	3.5 – 4	4.7 – 5.1	< 2	2.8 – 3.3
esomeprazole magnesium (Nexium, Nexium 24HR)	3.8	4.3	3.8 – 5.5	> 1
esomeprazole strontium				
lansoprazole (Prevacid)	2.1	1.4 – 7.4	≥ 1	1.3 – 3
omeprazole (Prilosec)[76]	5.2	3.7	6.9	4
omeprazole/sodium bicarbonate (Zegerid)[77]	0.4 – 5.2	1.9 – 3.7	2.4 – 6.9	0.9 – 4
pantoprazole (Protonix)	1 – 4	2 – 6	2 – 9	2
rabeprazole (Aciphex)	< 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 safety of esomeprazole strontium has been established from adequate and well-controlled studies of esomeprazole magnesium.

SPECIAL POPULATIONS[78,79,80,81,82,83,84,85]

Pediatrics

Safety and effectiveness of lansoprazole (Prevacid) have been established for the short-term (≤ 12 weeks) treatment of GERD and short-term treatment of erosive esophagitis in children aged 1 to 17 years. Esomeprazole magnesium (Nexium) is indicated for short-term treatment of GERD (ages 1 to 17 years) and the healing of erosive esophagitis (ages 1 to 11 years); esomeprazole magnesium (Nexium 24HR) available OTC is not indicated for use in pediatric patients unless under supervision of a healthcare provider. Omeprazole (Prilosec) is indicated for children ages 1 to 16 years for the short-term treatment of GERD and the maintenance of healing of erosive esophagitis. Omeprazole (Prilosec) is also indicated for short term treatment (6 weeks) of erosive esophagitis due to acid-mediated GERD in patients 1 month to less than 1 year of age. 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 5 years of age and older for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. Dexlansoprazole (Dexilant) is indicated for the healing of erosive esophagitis, maintenance of healed erosive esophagitis and relief of heartburn, and treatment of non-erosive GERD in children 12 years of age and older.

Safety and effectiveness of esomeprazole strontium has 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), esomeprazole strontium, and pantoprazole (Protonix) were classified as Pregnancy Category C, and all other agents, including esomeprazole magnesium (Nexium, Nexium 24HR), in the class were rated Pregnancy Category B; however, labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and now contains a description of the risk. Data is not sufficient on the use of these agents during pregnancy to inform of the risks of major birth defects or other adverse pregnancy outcomes.

Other Considerations

The clearance of PPIs may be reduced in patients with advanced age and those with mild to moderate liver disease.[86,87,88] 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.[89,90] 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 and use is not recommended for use in patients with severe hepatic impairment. Doses of esomeprazole (Nexium, Nexium 24HR) should not exceed 20 mg (equivalent to 24.65 mg of esomeprazole strontium) 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. The pharmacokinetics and safety of esomeprazole strontium has not been studied in patients with severe renal impairment and therefore is not recommended.

Genetic expression of CYP2C19 varies from person to person. As a result, a small subset of patients (13 to 23 percent of Asians, 2% to 6% of Caucasians) experience 2 to 4 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 4-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[91,92,93,94,95,96,97,98]

Drug	Adults	Pediatrics	Oral Availability
dexlansoprazole (Dexilant)	Erosive esophagitis (healing) – 60 mg capsule once daily for up to 8 weeks	Erosive esophagitis (healing) – Ages 12 years and older: 60 mg capsule once daily for up to 8 weeks	30 mg, 60 mg delayed-release capsules Dexlansoprazole may be given with applesauce, in water with an oral syringe, or via a nasogastric tube
	Erosive esophagitis (maintenance of healing) – 30 mg once daily (Controlled studies did not extend beyond 6 months)	Erosive esophagitis (maintenance of healing and treatment of heartburn) – Ages 12 to 17 years: 30 mg once daily (Controlled studies did not extend beyond 16 weeks)	
	Symptomatic non-erosive GERD – 30 mg once daily for 4 weeks	Symptomatic non-erosive GERD – Ages 12 years and older: 30 mg once daily for 4 weeks	
esomeprazole magnesium (Nexium), Esomep-EZS)	*H. pylori* eradication – 40 mg daily + clarithromycin 500 mg and amoxicillin 1 g twice daily for 10 days	Erosive Esophagitis (treatment) - Ages 1 to 11 years: Weight-based dosing < 20 kg: 10 mg daily for 8 weeks ≥ 20 kg: 10 to 20 mg daily for 8 weeks	20 mg, 40 mg delayed-release capsules 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg delayed-release powder for oral suspension (brand only) Nexium Delayed-Release Powder for Oral Suspension should be administered in water Esomep-EZS (esomeprazole kit) contains 30 esomeprazole 20 mg delayed-release capsules and a 59 mL moisturizing pill swallowing spray
	GERD – 20 mg or 40 mg daily for 4 weeks An additional 4 weeks may be considered if needed		
	Erosive esophagitis (treatment) – 20 mg or 40 mg daily for 4 to 8 weeks	GERD – Ages 1 to 11 years: 10 mg or 20 mg once daily for up to 8 weeks; Ages 12 to 17 years: 20 or 40 mg daily for up to 8 weeks	
	Erosive esophagitis (maintenance) – 20 mg daily (Controlled studies did not extend beyond 6 months)		
	Pathological hypersecretory conditions – 40 mg twice daily		
	Reduction of risk for NSAID-associated gastric ulcers – 20 mg or 40 mg daily for up to 6 months		
esomeprazole magnesium (Nexium 24HR)	Heartburn – 20 mg once daily in the morning. If frequent heartburn returns, may repeat a 14-day course of treatment every 4 months. If more frequent use is required, a healthcare provider should be consulted	--	20 mg delayed-release capsules (OTC)

Dosages (continued)

Drug	Adults	Pediatrics	Oral Availability
esomeprazole strontium	*H. pylori* eradication – 49.3 mg daily + clarithromycin 500 mg and amoxicillin 1 g twice daily for 10 days Erosive esophagitis (healing): 24.65 mg or 49.3 mg once daily for 4 to 8 weeks Erosive esophagitis (maintenance): 24.65 mg once daily (controlled studies did not extend beyond 6 months) Reduction of risk for NSAID-associated gastric ulcers – 24.65 mg or 49.3 mg daily for up to 6 months GERD – 24.65 mg once daily for 4 weeks Pathological hypersecretory conditions – 49.3 mg twice daily	--	24.65 mg and 49.3 mg delayed-release capsules of esomeprazole strontium (equivalent to 20 mg and 40 mg of esomeprazole, respectively) Delayed-release capsules should be swallowed whole and not chewed or crushed Delayed-release capsule may be opened and granules mixed with applesauce, in water with an oral syringe, or via a nasogastric tube
lansoprazole (Prevacid)	Duodenal ulcer (treatment) – 15 mg daily for 4 weeks Duodenal ulcer (maintenance) – 15 mg daily *H. pylori* eradication – 30 mg twice daily + clarithromycin 500 mg and amoxicillin 1 g twice daily for 10 to 14 days –OR– 30 mg 3 times a day + amoxicillin 1 g three times a day for 14 days Gastric ulcer – 30 mg daily for up to 8 weeks GERD – 15 mg daily for up to 8 weeks Erosive esophagitis (treatment) - 30 mg daily for up to 8 weeks An additional 8 weeks may be considered if needed Erosive esophagitis (maintenance) – 15 mg daily (Studies did not extend past 12 months) 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 4 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 8 weeks	GERD and Erosive esophagitis (treatment) – Ages 1 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 8 weeks Erosive Esophagitis (treatment) – Ages 12 to 17 years: 30 mg daily for up to 8 weeks	15 mg, 30 mg delayed-release capsules 15 mg, 30 mg delayed-release orally disintegrating tablets

Dosages (continued)

Drug	Adults	Pediatrics	Oral Availability
lansoprazole (Prevacid 24hr)	Heartburn – 15 mg daily for 14 days	--	15 mg delayed-release tablet
omeprazole (Prilosec)	Duodenal ulcer (Treatment) – 20 mg daily for up to 4 to 8 weeks	GERD (treatment up to 4 weeks) and Erosive Esophagitis (maintenance up to 12 months; treatment for 4 – 8 weeks): Ages 1 to 16 years old: Weight based dosing 5 kg to < 10 kg: 5 mg once daily 10 kg to < 20 kg: 10 mg once daily ≥ 20 kg: 20 mg once daily **Note:** On a per kg basis, the doses to heal erosive esophagitis in pediatric patients are greater than those for adults	10 mg, 20 mg, 40 mg delayed-release capsules 2.5 mg, 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 3 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 4 to 8 weeks		
	GERD – 20 mg daily for up to 4 weeks	Erosive Esophagitis (treatment up to 6 weeks): Ages 1 month to less than 1 year of age: Weight based dosing 3 kg to < 5 kg: 2.5 mg once daily 5 kg to < 10 kg: 5 mg once daily ≥ 10 kg: 10 mg once daily	
	Erosive esophagitis (treatment) – 20 mg daily for 4 to 8 weeks		
	Erosive esophagitis (maintenance) – 20 mg daily		
	Pathological hypersecretory conditions – 60 mg daily (Doses up to 120 mg 3 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 5 years)		
omeprazole magnesium OTC (Prilosec OTC) omeprazole OTC	Heartburn – 20 mg once daily in the morning; if frequent heartburn returns, may repeat a 14-day course of treatment every 4 months; if more frequent use is required, a healthcare provider should be consulted	--	20 mg delayed-release tablet 20 mg delayed-release orally disintegrating tablet (ODT)

Dosages (continued)

Drug	Adults	Pediatrics	Oral Availability
omeprazole/ sodium bicarbonate (Zegerid)	Duodenal ulcer (treatment) – 20 mg daily for 4 weeks; An additional 4 weeks may be considered if needed	--	20 mg and 40 mg immediate-release capsules (Each capsule contains 1,100 mg sodium bicarbonate) 20 and 40 mg oral suspension packet (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 to 2 tablespoons of water; Do not use other liquids or foods
	Gastric ulcer – 40 mg daily for 4 to 8 weeks		
	GERD – 20 mg daily for up to 4 weeks		
	Erosive esophagitis (treatment) – 20 mg daily for 4 to 8 weeks		
	Erosive esophagitis (maintenance) – 20 mg daily for 4 to 8 weeks		
	Reduction of risk of upper GI bleeding in critically ill patients (40 mg oral suspension only) – 40 mg initially, followed by 40 mg 6 to 8 hours later and 40 mg daily thereafter for 14 days		
omeprazole/ sodium bicarbonate OTC (Zegerid OTC)	Heartburn – 1 capsule daily for 14 days; An additional 14 day course may be repeated every 4 months	--	20 mg/ 1,100 mg capsules
pantoprazole (Protonix)	Erosive esophagitis (treatment) due to GERD – 40 mg daily for up to 8 weeks; An additional 8 weeks may be considered if needed	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 8 weeks ≥ 40 kg: 40 mg once daily up to 8 weeks	20 mg, 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
	Erosive esophagitis (maintenance) due to GERD – 40 mg daily (Studies did not extend past 12 months)		
	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 2 years)		

Dosages (continued)

Drug	Adults	Pediatrics	Oral Availability
rabeprazole (Aciphex)	Duodenal ulcer (treatment) – 20 mg daily for up to 4 weeks; A few patients may require additional therapy to achieve healing.	GERD – Ages 1 to 11 years (Sprinkles) Less than 15 kg: 5 mg once daily for up to 12 weeks with the option to increase to 10 mg if inadequate 15 kg or more: 10 mg once daily for up to 12 weeks Ages 12 years and older (tablets): 20 mg daily for up to 8 weeks	5 mg, 10 mg delayed-release capsules (Sprinkles) 20 mg delayed-release tablets
	H. pylori eradication – 20 mg twice daily + clarithromycin 500 mg and amoxicillin 1 g twice daily for 7 days		
	GERD – 20 mg daily for 4 weeks; An additional 4 weeks may be considered if needed		
	Erosive esophagitis (treatment) – 20 mg daily for 4 to 8 weeks; An additional 8 weeks may be considered if needed		
	Erosive esophagitis (maintenance) – 20 mg daily (Studies did not extend past 12 months)		
	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 1 year)		

The ACG advises that PPI therapy should be initiated at once a day dosing, before the first meal of the day. For patients with partial response to once daily therapy, tailored therapy with adjustment of dose timing and/or twice daily dosing should be considered in patients with night-time symptoms, variable schedules, and/or sleep disturbance.[99]

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% 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 3 days, primary outcome studied not of clinical relevance, use of formulations not included in this review, unapproved dosing regimens, and results measured by survey.

The literature review of significant trials comparing agents within this therapeutic class is complete as of February 17, 2020. Only published comparative studies are included below.

The safety and efficacy of esomeprazole strontium was established based on adequate and well-controlled adult studies of esomeprazole magnesium.[100]

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.[101] No differences in healing rates between the groups either after 2 weeks (86.2% for lansoprazole and 82.1% for omeprazole) or after four weeks (97.1% and 96.2%, 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.[102] 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 4 weeks were 93.9% with lansoprazole and 97.5% with omeprazole, with no significant differences between groups. Endoscopic relapse rates after 6 months were 4.5% with lansoprazole 15 mg, 0% with lansoprazole 30 mg, and 6.3% with omeprazole 20 mg, compared with 3.3%, 0%, and 3.5%, respectively, at 12 months. There were no significant differences among groups. The incidence of adverse events during acute treatment was 6% and 7.1% in the lansoprazole and omeprazole groups, respectively. During maintenance therapy, adverse events occurred in 12.2% of patients treated with lansoprazole 15 mg, 5.6% with lansoprazole 30 mg, and 11% with omeprazole 20 mg.

rabeprazole (Aciphex) versus omeprazole (Prilosec)

A randomized, double-blind, multicenter study compared the efficacy and tolerability of rabeprazole and omeprazole in patients with active duodenal ulcers.[103] Patients with active duodenal ulcer received rabeprazole 20 mg (n=102) or omeprazole 20 mg (n=103) once daily for 2 or 4 weeks with ulcer healing monitored by endoscopy. After 2 weeks, complete ulcer healing after 2 weeks was documented in 69% of patients given rabeprazole and in 62% of patients given omeprazole (p=0.083). After 4 weeks, healing rates were 98% in the rabeprazole group and 93% 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 4-week treatment period. The study concluded that rabeprazole produced healing rates equivalent to omeprazole at weeks 2 and 4.

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 5 millimeters long.[104] Grade B esophagitis has one or more isolated mucosal breaks greater than 5 millimeters in length. Grade C involves 1 or more mucosal breaks bridging the tops of folds in the esophagus but involving less than 75% of the circumference. Grade D esophagitis is one or more mucosal breaks bridging the tops of folds and involving greater than 75% of the esophageal circumference.

dexlansoprazole (Dexilant) versus lansoprazole (Prevacid)

In 2 multicenter, double-blind, active-controlled, randomized, 8-week studies, 4,092 patients with endoscopically confirmed erosive esophagitis (EE) were randomized to 1 of the following 2 treatment groups: dexlansoprazole 60 mg daily, dexlansoprazole 90 mg daily, or lansoprazole 30 mg daily.[105] Based on the Los Angeles Classification Grading System (Grades A-D), 71% of patients had mild EE (Grades A and B) and 29% 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% of patients, respectively, that received dexlansoprazole 60 mg experienced healing at week 4, compared to 65% of patients, in both studies who received lansoprazole. At week 8, 87% and 85% of patients in studies 1 and 2, respectively, that received dexlansoprazole 60 mg experienced healing, compared to 85% and 79% of patients receiving lansoprazole. Non-inferiority was demonstrated in both studies. Dexlansoprazole 90 mg did not provide additional clinical benefit over dexlansoprazole 60 mg.

esomeprazole magnesium (Nexium) versus lansoprazole (Prevacid)

A multicenter, randomized, double-blind, parallel-group trial compared esomeprazole magnesium with lansoprazole for healing of erosive esophagitis and resolution of heartburn.[106] 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 8 weeks. The primary efficacy endpoint was healing of erosive esophagitis at week 8. Secondary assessments included proportion of patients healed at week 4, 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%) than lansoprazole 30 mg (88.8%) at week 8 (p=0.0001). A significant difference in healing rates favoring esomeprazole was also observed at week 4. 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 magnesium 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.[107] Patients received esomeprazole 40 mg (n=498) or lansoprazole 30 mg (n=501) once daily for up to 8 weeks. The primary end point was erosive esophagitis healing through week 8. Secondary assessments included investigator-assessed resolution of symptoms and safety and tolerability. Estimated healing rates at week 8 were 82.4% with esomeprazole and 77.5% with lansoprazole. Heartburn resolved at week 4 in 72% and 64% 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.[108] Patients with Los Angeles grades C and D erosive esophagitis at baseline were

randomized to treatment with either esomeprazole magnesium 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 6 months. Esophago-gastroduodenoscopies were completed at months 3 and 6, and investigators assessed symptom severity at months 1, 3, and 6. Estimated endoscopic/symptomatic remission rate during a period of 6 months was significantly higher (p=0.0007) for patients who received esomeprazole 20 mg once daily (84.8%) compared with those who received lansoprazole 15 mg (75.9%). There were no significant differences between treatments for reflux symptoms. Both treatments were well tolerated.

esomeprazole magnesium (Nexium) versus omeprazole (Prilosec)

The study was designed to evaluate the efficacy and tolerability of esomeprazole magnesium relative to omeprazole in healing erosive esophagitis and resolving accompanying symptoms of GERD.[109] 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 8-week, multicenter, randomized, double-blind, parallel-group study. The primary efficacy endpoint was the proportion of patients with healed esophagitis at 8 weeks. Secondary endpoints were the proportion of patients healed at week 4, resolution of heartburn at week 4, 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 8 (93.7% versus 84.2%, respectively; p<0.001). Healing rates at week 4 were 81.7% and 68.7%, respectively. Secondary outcome measures favored esomeprazole. Tolerability and safety of esomeprazole are comparable to omeprazole.

To compare esomeprazole magnesium 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 8 weeks in a multicenter, double-blind, parallel-group trial.[110] The primary outcome was the proportion of patients with healed erosive esophagitis at week 8. At week 8, estimated healing rates were 92.2% (95% CI, 89.9 to 94.5) with esomeprazole and 89.8% (95% CI, 87.2- to 92.4) with omeprazole. The treatments showed comparable tolerability profiles.

A similarly designed, multicenter, double-blind, parallel-group, 8-week study compared low-dose esomeprazole magnesium 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.[111] The primary outcome of the study was the proportion of patients with healed EE through week 8. Secondary outcomes included diary and investigator assessments of heartburn symptoms. Cumulative life-table healing rates at week 8 were similarly high for esomeprazole 20 mg (90.6%; 95% CI, 88.1 to 93) and omeprazole 20 mg (88.3%; 95% CI, 85.5 to 91). Both treatments were comparable for other secondary measures and had similar tolerability profiles.

Esomeprazole magnesium 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.[112] The primary efficacy variable was the proportion of patients healed at week 8. Secondary variables included healing and heartburn resolution at week 4, time to first resolution and sustained resolution of heartburn, and% of heartburn-free days and nights. Significantly more patients were healed at week 8 with esomeprazole 40 mg (94.1%) and 20 mg (89.9%) compared to omeprazole 20 mg (86.9%) (each p<0.05). Esomeprazole 40

mg was also significantly more effective than omeprazole for healing at week 4 and for all secondary variables evaluating heartburn resolution. Tolerability was similar in all groups.

esomeprazole magnesium (Nexium) versus pantoprazole (Protonix)

In the 8-week EXPO study, the efficacy of esomeprazole magnesium 40 mg versus pantoprazole 40 mg for healing erosive esophagitis in 3,151 patients with a history of symptomatic GERD (6 months or more) and heartburn on at least 4 of the 7 days preceding enrollment was examined.[113] Endoscopies were performed to grade erosive esophagitis severity using the Los Angeles (LA) classification system at baseline, 4 weeks, and 8 weeks (if unhealed at 4 weeks). Heartburn severity was recorded by patients on diary cards. The primary end point was healing of erosive esophagitis by week 8 of treatment. Esomeprazole 40 mg healed a significantly greater proportion of erosive esophagitis patients than pantoprazole 40 mg at both 4 weeks (esomeprazole 81%, pantoprazole 75%, $p<0.001$) and 8 weeks (esomeprazole 96%, pantoprazole 92%, $p<0.001$). The median time to reach sustained heartburn resolution was 6 days in patients receiving esomeprazole and 8 days with pantoprazole ($p<0.001$).

In the 6-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 magnesium 20 mg or pantoprazole 20 mg for up to 8 weeks.[114] The study was double-blinded. Patients free of moderate/severe heartburn and acid regurgitation and with healed erosive esophagitis at 4 to 8 weeks continued the assigned treatment regimen into a 6-month maintenance therapy phase of the study. Following 6 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%; $p<0.0001$). 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%, respectively; $p<0.001$).

Gastric Ulcer

rabeprazole (Aciphex) versus omeprazole (Prilosec)

A randomized, double-blind, multicenter study compared rabeprazole and omeprazole in patients with active gastric ulcers.[115] Two hundred twenty-seven patients were randomized to receive either rabeprazole 20 mg (n=113) or omeprazole 20 mg (n=114) once daily for 3 or 6 weeks, with healing monitored by endoscopy. After 3 weeks, complete healing was documented in 58% of rabeprazole patients and 61% of omeprazole patients (p=NS). After 6 weeks, healing rates were identical in both groups at 91%. Differences in symptom relief significantly favored rabeprazole at week 3 for daytime pain improvement ($p=0.023$), at week 6 for pain frequency ($p=0.006$), and complete resolution of night pain ($p=0.022$). Both drugs were well-tolerated over the 6-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.[116] Treatment was administered for 4 weeks and extended another 4 weeks if the ulcer had not healed. After 4 weeks, complete ulcer healing was seen in 88% of pantoprazole patients and 77% of patients treated with omeprazole ($p<0.05$). At 8 weeks, the corresponding values were 97% and 96%, 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 1 or more erosions in 1 mucosal fold of the esophagus. Grade II has 1 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.[117] The treatment period was 4 or 8 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 4 or 8 weeks of treatment. Patients receiving lansoprazole experienced a greater improvement in heartburn after 4 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 8 weeks.[118] Healing was evaluated endoscopically. Healing rates at 2, 4, 6, and 8 weeks were 65.3%, 83.3%, 89.4%, and 90%, respectively, for lansoprazole 30 mg; 56.3%, 74.6%, 80.3%, and 78.8% for lansoprazole 15 mg; 60.9%, 82%, 89.7%, and 90.7% for omeprazole 20 mg; and 23.9%, 32.8%, 36.6%, and 40% 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 4, 6, and 8 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.[119] The trial enrolled 211 patients. Healing was assessed by endoscopy after 4 weeks and, if necessary, 8 weeks. Symptom relief was determined by symptom assessments at the same time points. There were no significant differences in healing after 4 weeks (87.5% for lansoprazole, 80.6% for omeprazole; 95% CI, -4 to +17.8) or overall healing (96.1% for lansoprazole, 93.1% for omeprazole; 95% CI, -4.2 to +10.2) between the 2 groups. Relief of reflux-related symptoms at 4 and 8 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 4 and 8 weeks of administration.[120] Four-hundred sixty-one patients were included in the prospective, randomized, multicenter double-blind study. The difference in healing rates at 4 and 8 weeks were not statistically significant. Healing rates at 4 weeks were 81% and 80% in the pantoprazole and lansoprazole groups, respectively, and 90% and 86% at 8 weeks, respectively. The heartburn relief rates at day 14 were 88% and 86% in the pantoprazole and lansoprazole groups, respectively.

pantoprazole (Protonix) versus esomeprazole magnesium (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 magnesium daily.[121] Endoscopically verified healing was assessed at the first and final visit (after 4, 6, 8, or 10 weeks of treatment). Overall healing in the treatment groups was 95% (pantoprazole) and 90% (esomeprazole); rates were not statistically significantly different. Pantoprazole and esomeprazole demonstrated comparable safety and tolerability.

The efficacy of pantoprazole 20 mg and esomeprazole magnesium 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.[122] During the acute phase (initial 28 days), 236 patients received pantoprazole 20 mg once daily. Patients without heartburn (n=199) during the final 3 days of the acute phase were eligible to enter the long-term phase of 6 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 2 treatment groups. The combined symptom score of the 3 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.[123] Patients underwent endoscopy upon study entrance and again after 4 weeks, and continued to receive an additional 4 weeks of treatment if esophagitis was not resolved. After 4 weeks of treatment, complete healing occurred in 74% of patients in the pantoprazole group and 78% patients in the omeprazole group. At 8 weeks, the respective healing rates were 90% and 94%. 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% of patients treated with omeprazole showed improvement at 2 weeks and 83% and 86%, respectively, at 4 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.[124] Patients received rabeprazole 20 mg once daily (n=100) or omeprazole 20 mg (n=102) once daily for 4 or 8 weeks, with healing verified by endoscopy. GERD healing rates evaluated at weeks 4 and 8 were equivalent. Four-week healing rates for rabeprazole and omeprazole were 81% and 81%, respectively, and 92% and 94%, respectively, at 8 weeks. Both drugs were well tolerated over the 8-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.[125]

Patients were randomized to receive rabeprazole 10 mg 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 5%, 4%, and 5% 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 2 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 4 weeks each with omeprazole 20 mg and rabeprazole 20 mg.[126] At the end of 8 weeks, patients compared the 2 medications using 7 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 1 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 2 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 1 adverse event. Patients indicated the most important drug characteristics for treating this condition were rapid and lasting control of pain. Most (83.6%) 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 3, 7, or 10 days or omeprazole 20 mg twice daily for 10 days.[127] In addition, all patients received concurrent amoxicillin 1 gm and clarithromycin 500 mg twice daily. *H. pylori* eradication rates were significantly lower for the 3-day rabeprazole regimen (27%) than in the 7 (77%), or 10 day (78%) courses of rabeprazole or the 10-day course of omeprazole (73%). There was no significant difference between the 7 or 10 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*.[128] 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% 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%). In patients receiving clarithromycin and metronidazole, rabeprazole produced a lower, but not statistically significant, eradication rate than omeprazole (79% versus 86%). Ulcer healing rates were higher than 90% with *H. pylori* eradication. All regimens were well tolerated.

META-ANALYSES

A systematic literature search using PubMed, Embase, and Cochrane Library identified 25 randomized controlled trials (n=25,088) from inception to November 2016 that compared treatment for a least 4 weeks of continuous therapy with FDA-approved PPIs in adults with erosive esophagitis.[129] Studies assessing esophageal strictures or Barrett's esophagus were excluded. Comparisons included dexlansoprazole 60 mg, esomeprazole 40 mg, esomeprazole 20 mg, pantoprazole 40 mg, lansoprazole 30 mg, rabeprazole 20 mg, and omeprazole 20 mg (which was the most often used as the control intervention). The primary efficacy outcome was the endoscopic healing rates at 4 and 8 weeks. As compared to omeprazole 20 mg, esomeprazole 40 mg provided significantly healing rates at 4 weeks [odds ratio (OR), 1.46 (95% CI, 95% CI, 1.24 to 1.71)] and 8 weeks (OR, 1.58; 95% CI, 1.29 to 1.92). Esomeprazole 40 mg provided significantly healing rates when compared to lansoprazole 30 mg at 4 weeks (OR, 1.3; 95% CI, 1.1 to 1.53) and 8 weeks (OR, 1.37; 95% CI, 1.13 to 1.67). Compared to rabeprazole 20 mg, esomeprazole provided greater healing at week 4 (OR, 1.64; 95% CI, 1.1 to 2.44) and week 8 (OR, 2.02; 95% CI, 1.25 to 3.27). Compared to pantoprazole 40 mg, esomeprazole 40 mg provided greater healing at week 4 (OR, 1.31; 95% CI, 1.1 to 1.58) and week 8 (OR, 1.2; 95% CI, 0.96 to 1.5). The meta-analysis showed no significant difference for the remaining PPIs in comparison to each other.

A total of 24 randomized controlled trials (n=6,188) were included in a network meta-analysis. The literature search used Medline, Embase, Cochrane Library, ClinicalTrails.gov, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBM).[130] The study included comparisons between omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. The network meta-analysis demonstrated a significant differences in 4-week healing rate of duodenal ulcer for pantoprazole 40 mg compared to lansoprazole 15 mg (relative risk [RR], 3.57; 95% CI, 1.36 to 10.31) and lansoprazole 30 mg versus lansoprazole 15 mg (RR, 2.45; 95% CI, 1.01 to 6.14). While, pantoprazole 40 mg was more effective when compared with other regimens, the differences were not significant. The study also suggested that lansoprazole 15 mg had a lower healing rate compared to other regimens. No significant differences were seen when comparing other PPIs.

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 magnesium (Nexium), esomeprazole strontium, 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 magnesium (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 magnesium (Nexium), omeprazole/sodium bicarbonate (Zegerid), and pantoprazole (Protonix) are available as formulations intended for use as suspensions.

Except for dexlansoprazole (Dexilant), esomeprazole magnesium OTC (Nexium 24 HR), 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 7-day course of treatment while esomeprazole magnesium

(Nexium), esomeprazole strontium, lansoprazole (Prevacid), and omeprazole (Prilosec) require 10 to 14 days of treatment.

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