Therapeutic Class Overview
Proton Pump Inhibitors

INTRODUCTION

- The proton pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally considered the most potent acid suppressants available. Parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to several stimuli. Within the parietal cell, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K^+) for hydrogen ions (H^+) resulting in a lower gastric pH. The PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. The PPIs can only inhibit proton pumps that are actively secreting acid (*Wolfe et al, 2000*). Approximately 70% to 80% of the proton pumps will be active following a meal (*Welage, 2003*). As a result, single doses of PPIs will not completely inhibit acid secretion, and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. With regular dosing, maximal acid suppression occurs in 3 to 4 days (*Welage, 2003; Wolfe et al, 2000*).
- There are currently 6 PPIs available on the market in a variety of formulations. The PPIs include dexlansoprazole (Dexilant), esomeprazole magnesium (Nexium, Nexium IV, Nexium 24HR), lansoprazole (Prevacid, Prevacid Solutab, Prevacid 24HR), omeprazole (Prilosec, Prilosec OTC, Zegerid, Zegerid OTC), pantoprazole (Protonix, Protonix IV), and rabeprazole (Aciphex, Aciphex Sprinkle), of which certain formulations of rabeprazole, esomeprazole, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are available generically. An alternative salt form of esomeprazole, esomeprazole strontium, was previously available, but has since been discontinued. In addition, lansoprazole, esomeprazole magnesium, omeprazole, and omeprazole with sodium bicarbonate are available over-the-counter (OTC). The only currently available PPI combination product is naproxen/esomeprazole (Vimovo); however, combination products are outside the scope of this overview and will not be reviewed.
- All of the PPIs are substituted benzimidazole derivatives and are structurally related.
  - Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole contains only the *S*-isomer of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer.
  - Dexlansoprazole, the enantiomer of lansoprazole, has a dual delayed-release formulation designed to provide 2 separate releases of medication. It contains 2 types of enteric-coated granules resulting in a concentration-time profile with 2 distinct peaks: the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours. In addition, it can be taken without regard to meals (*Dexilant prescribing information, 2018*).
- The PPIs primarily differ in their pharmacokinetic and pharmacodynamic properties in addition to their formulations. While some differences have been reported in head-to-head studies directly comparing the PPIs, the magnitude of these differences is generally small, and the clinical significance has not been established. When administered in equivalent dosages, the PPIs have generally demonstrated comparable efficacy to one another (*Dean, 2010*).
- In general, all PPIs are FDA-approved for the treatment of gastroesophageal reflux disease (GERD) and for the healing and maintenance of erosive esophagitis. Some of the agents also have approval for the treatment of peptic ulcer disease, the treatment of pathological hypersecretory conditions, and *Helicobacter pylori (H. pylori)* eradication as part of combination therapy with antibiotics.
- Current national and international consensus guidelines recognize the PPIs as first-line therapy for the management of dyspepsia, GERD, peptic ulcer disease, and eradication of *H. pylori.* In addition, these agents have a role in the management of Barrett's esophagus. Most currently available guidelines do not give preference to one PPI over another (*American Gastroenterological Association [AGA], 2011; Chey et al, 2017; Kahrilas et al, 2008; Katz et al, 2013; Laine et al, 2012; Lanza et al, 2009; Malfertheiner et al, 2017; Moayyedi et al, 2017; Rosen et al, 2018; Shaheen et al, 2016*). The 2016 joint European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guideline for management of *H. pylori* in children and adolescents states that esomeprazole and rabeprazole may be preferred when available, because they are less susceptible to degradation by rapid CYP2C19 metabolizers (*Jones et al, 2017*). However, the American Academy of Pediatrics does not recommend routine use of PPIs in preterm infants for GERD due to a lack of evidence of PPI efficacy in this population as well as evidence of significant adverse effects (*Eichenwald 2018*).

- The agents included in this review are listed alphabetically by brand name in Table 1. Since there are multiple branded agents that contain the same generic component(s), the remaining tables in the review are organized alphabetically by generic name.
- Medispan class: Gastrointestinal Agents; Ulcer drugs/antispasmodics/anticholinergics; Proton pump inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aciphex (rabeprazole sodium) delayed-release tablets	✔
Aciphex Sprinkle (rabeprazole sodium) delayed-release capsules§	✔
Dexilant (dexlansoprazole) delayed-release capsules	-†
esomeprazole magnesium* delayed-release capsules	✔
lansoprazole* delayed-release orally disintegrating tablets	✔
Nexium (esomeprazole magnesium) delayed-release capsules	✔
Nexium (esomeprazole magnesium) granules for delayed-release oral suspension	-
Nexium IV (esomeprazole sodium) injection	✔
Nexium 24HR* (esomeprazole magnesium) delayed-release capsules	✔
Nexium 24HR* (esomeprazole magnesium) delayed-release tablets	-
omeprazole magnesium* delayed-release capsules, tablets, disintegrating tablet	✔
Prevacid (lansoprazole) delayed-release capsules	✔
Prevacid 24HR* (lansoprazole) delayed-release capsules	✔
Prevacid Solutab (lansoprazole) delayed-release orally disintegrating tablets	✔
Prilosec (omeprazole magnesium) oral packet	-
Prilosec OTC* (omeprazole magnesium) delayed-release tablets	✔
Protonix (pantoprazole) delayed-release tablets	✔
Protonix (pantoprazole) powder for delayed-release oral suspension	-
Protonix IV (pantoprazole) injection, powder for solution	✔
Zegerid (omeprazole with sodium bicarbonate) capsules‡	✔
Zegerid (omeprazole with sodium bicarbonate) powder for oral suspension	✔
Zegerid OTC* (omeprazole with sodium bicarbonate) capsules, oral suspension	✔

*Available OTC.
†Generic 60 mg delayed-release capsule approved by the FDA for adult patients, but generic product not yet available due to patent exclusivity.
‡A branded generic product, Omeppi, which contains the same ingredients as Zegerid capsules, is also available.
§ Generic only available in 10 mg strength

(*DRUGS@FDA.com, 2020; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2020; Clinical Pharmacology 2020*)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Dexlansoprazole	Esomeprazole magnesium	Esomeprazole sodium	Lansoprazole	Omeprazole magnesium	Omeprazole/ sodium bicarbonate	Pantoprazole	Rabeprazole
GERD*								
Maintaining healing of erosive esophagitis	✔	✔		✔	✔	✔	✔	✔
Treatment of erosive esophagitis	✔	✔	✔	✔	✔	✔	✔ ‡	✔
Treatment of symptomatic GERD	✔	✔		✔	✔	✔		✔
Peptic Ulcer Disease								
Healing of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcer				✔				
H. pylori eradication to reduce the risk of duodenal ulcer recurrence		✔ †		✔ †	✔ †			✔ †
Maintenance of healing duodenal ulcers				✔				
Risk reduction of NSAID-associated gastric ulcer		✔		✔				
Treatment of active, benign gastric ulcer				✔	✔	✔		
Treatment of active duodenal ulcers				✔	✔	✔		✔
Other								
Risk reduction of upper gastrointestinal bleeding in critically ill patients						✔ (oral suspension)		
Treatment of frequent heartburn for up to 14 days		✔ (Nexium 24HR)		✔ (Prevacid 24HR)	✔ (Prilosec OTC)	✔ (Zegerid OTC)		
Treatment of pathological hypersecretory conditions,		✔		✔	✔		✔ §	✔

Indication	Dexlansoprazole	Esomeprazole magnesium	Esomeprazole sodium	Lansoprazole	Omeprazole magnesium	Omeprazole/ sodium bicarbonate	Pantoprazole	Rabeprazole
including Zollinger-Ellison syndrome								
Risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults			✔					

a Esomeprazole magnesium/sodium, lansoprazole, omeprazole, pantoprazole, and rabeprazole (Aciphex Sprinkle) are approved for pediatric patients. Dexlansoprazole and rabeprazole (Aciphex) are indicated for patients 12 years of age or older. Omeprazole/sodium bicarbonate is approved for adult patients.
b As triple therapy in combination with amoxicillin and clarithromycin (esomeprazole magnesium, lansoprazole, omeprazole, and rabeprazole) or dual therapy with amoxicillin (lansoprazole) or clarithromycin (omeprazole).
c Oral formulations indicated for the short-term treatment of erosive esophagitis associated with GERD; intravenous formulation indicated for the short-term treatment (7 to 10 days) of adult patients with GERD associated with a history of erosive esophagitis.
d Intravenous and oral formulation.

(*Prescribing information: Aciphex, 2019; Aciphex Sprinkle, 2018; Dexilant, 2018; lansoprazole, 2018; Nexium, 2018; Nexium IV, 2019; Nexium 24HR, 2019; Prevacid, 2018; Prevacid 24HR, 2019; Prilosec suspension, 2018; Prilosec OTC, 2019; Protonix, 2019; Protonix IV, 2019; Zegerid, 2019; Zegerid OTC, 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials consistently demonstrate that the PPIs are highly effective in treating, providing symptom relief, and preventing relapse in gastric acid disorders such as GERD and peptic ulcer disease (*Armstrong et al, 2004; Bardhan et al, 2001; Bazzoli et al, 1998; Caro et al, 2001; Castell et al, 2002; Castell et al, 2005; Chan et al, 2010; Chey et al, 2003; Choi et al, 2007; Conrad et al, 2005; Delchier et al, 2000; Devault et al, 2006; Edwards et al, 2001; Fass et al, 2009; Fass et al, 2011; Fass et al, 2012; Felga et al, 2010; Fennerty et al, 2005; Fujimoto et al, 2011; Gisbert et al, 2003; Gisbert et al, 2004[a]; Gisbert, et al, 2004[b]; Goh et al, 2007; Haddad et al, 2013; Howden et al, 2002; Howden et al, 2009; Hsu et al, 2005; Kahrilas et al, 2000; Katz et al, 2007; Kinoshita et al, 2011; Klok et al, 2003; Labenz et al, 2005[a]; Labenz et al, 2005[b]; Laine et al, 2011; Lauritsen et al, 2003; Liang et al, 2017; Lightdale et al, 2006; McNicholl et al, 2012; Metz et al, 2009; Mönnikes et al, 2012; Pace et al, 2005; Pilotto et al, 2007; Pouchain et al, 2012; Ramdani et al, 2002; Regula et al, 2006; Richter et al, 2001[a]; Richter et al, 2011[b]; Scheiman et al, 2011; Schmitt et al, 2006; Scholten et al, 2003; Sharma et al, 2001; Sharma et al, 2009; Sugano et al, 2011; Tsai et al, 2004; Ulmer et al, 2003; van Pinxteren et al, 2010; Vergara et al, 2003; Wang et al, 2006; Wu et al, 2007*).
- A number of studies have compared the various PPIs to one another. While some differences have been reported, the magnitude of differences has been small and of uncertain clinical importance. In particular, the degree to which any of the reported differences would justify the selection of one versus another PPI, particularly when considering cost-effectiveness, is unclear (*Wolfe, 2020*).

GERD

- In meta-analyses and direct comparator trials, lansoprazole, omeprazole, pantoprazole, and rabeprazole have demonstrated comparable healing rates, maintenance of healing, and/or symptomatic relief of GERD (*Bardhan et al, 2001; Caro et al, 2001; Edwards et al, 2001; Klok et al, 2003; Pace et al, 2005; Sharma et al, 2001*). Furthermore, Richter et al reported that lansoprazole produced a significantly quicker and greater symptomatic relief of GERD compared to omeprazole; however, the absolute differences between the 2 treatments were small, and the clinical impact of the difference was not measured within the clinical trial (*Richter et al, 2001[b]*).
- The results of several meta-analyses and clinical trials demonstrated that esomeprazole may provide higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole, and pantoprazole at 4 and 8 weeks (*Castell et al, 2002; Devault et al, 2006; Edwards et al, 2001; Kahrilas et al, 2000; Klok et al, 2003; Labenz et al, 2005[a]; Labenz et al, 2005[b]; Li et al, 2017[a]; Richter et al, 2001[a]*). Subgroup analyses of 2 trials noted higher healing rates with esomeprazole in patients with more severe disease (*Labenz et al, 2005[a]; Schmitt et al, 2006*).
- Close analyses of all of these trials demonstrate that the overall differences between the various PPI agents were generally small and the clinical significance is not clear. In addition, results of these trials have not been consistently demonstrated in other clinical trials, particularly in those evaluating lansoprazole and pantoprazole (*Armstrong et al, 2004; Chey et al, 2003; Goh et al, 2007; Howden et al, 2002; Lightdale et al, 2006; Scholten et al, 2003*).

Peptic Ulcer Disease

- Meta-analyses and head-to-head trials comparing various PPIs for the treatment of peptic ulcer disease with *H. pylori* demonstrated comparable rates of eradication when paired with comparable antibiotic regimens (*Bazzoli et al, 1998; Choi et al, 2007; Gisbert et al, 2003; Gisbert et al, 2004[a]; Gisbert, et al 2004[b]; Ulmer et al, 2003; Vergara et al, 2003; Wang et al, 2006; Wu et al, 2007*).
- Results from 2 meta-analyses suggested that both esomeprazole- and rabeprazole-based *H. pylori* regimens were more effective with regard to eradication rates compared to traditional PPI-based regimens (lansoprazole, omeprazole, and pantoprazole) (*McNicholl et al, 2012; Xin et al, 2016*).

CLINICAL GUIDELINES

- Current consensus among various national and international treatment guidelines recommend a PPI as the first-line therapy in the treatment and maintenance of healed erosive esophagitis, symptomatic GERD, dyspepsia (patients ≤ 55 years and no alarm features), and peptic ulcer disease caused by NSAID therapy. Triple and quadruple combination therapy with antibiotics and a PPI are considered first-line therapy for peptic ulcer disease caused by *H. pylori*. Most of the treatment guidelines do not recommend one PPI over another, and no treatment guideline recommends one formulation of a PPI over another (*American Gastroenterological Association, 2011; Chey et al, 2017; Kahrilas et al,*

2008; Katz et al, 2013; Laine et al, 2012; Lanza et al, 2009; Malfertheiner et al, 2017; Moayyedi et al, 2017; Rosen et al, 2018; Shaheen et al, 2016). The 2016 joint ESPGHAN/NASPGHAN guideline for management of *H. pylori* in children and adolescents states that esomeprazole and rabeprazole may be preferred when available, because they are less susceptible to degradation by rapid CYP2C19 metabolizers (*Jones et al, 2017*).

- According to the AGA medical position statement on the management of GERD (2008) and the American College of Gastroenterology (ACG) guideline for the diagnosis and management of GERD (2013), PPIs are considered the drug of choice in the treatment of GERD with H_2-receptor antagonists as alternative agents that can be used for maintenance of GERD symptoms without erosive disease (*Kahrilas, 2008; Katz et al, 2013*). The ACG medical position statement notes that there are no major differences between the different PPIs (*Katz et al, 2013*).
- According to joint recommendations from NASPGHAN and ESPGHAN (2018), PPIs are recommended as first-line therapy for the treatment of reflux-related erosive esophagitis in infants and children with GERD. For children with GERD with typical symptoms, a 4- to 8-week course of H_2-receptor antagonists or PPIs is recommended. Patients with asthma and typical GERD symptoms should also be treated (*Rosen et al, 2018*). The American Academy of Pediatrics does not recommend routine use of PPIs in preterm infants for GERD. The 2018 guidance highlights the lack of evidence of PPI efficacy in this population as well as evidence of significant adverse effects (*Eichenwald 2018*).
- According to the ACG guideline for prevention of NSAID-related ulcer complications (2009), misoprostol or high-dose PPI treatment is recommended as co-therapy with anti-inflammatory analgesics in certain patients with high- and moderate-NSAID gastrointestinal risk. In patients who require both anti-inflammatory analgesics and low-dose aspirin, naproxen with either misoprostol or a PPI is also recommended (*Lanza et al, 2009*).
- According to the ACG guideline on the management of *H. pylori* infection (2017), there are many first-line options for *H. pylori* treatment; a regimen should be based on patient allergies, previous macrolide exposure, and known *H. pylori* resistance rates. A PPI, clarithromycin, and amoxicillin or metronidazole (clarithromycin-based triple therapy) regimen for 14 days is recommended where *H. pylori* clarithromycin resistance is known to be < 15%. Alternately, bismuth quadruple therapy, consisting of a PPI, bismuth, tetracycline, and a nitroimidazole (metronidazole or tinidazole) for 10 to 14 days should be considered as a first-line therapy option for areas of high clarithromycin resistance (*Chey et al, 2017*).
- High-dose PPIs are often used as primary long-term therapy in Zollinger-Ellison syndrome. PPIs are considered generally safe, even at high doses, and have demonstrated superior acid suppression, healing rates, and symptom relief compared with other antisecretory therapies (*Bergsland, 2018; National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] website*).
- A 2015 clinical guideline by the ACG also recognized the use of PPIs in the management of Barrett's esophagus; long-term PPI use will likely produce a net benefit for these patients (*Freedberg et al, 2017; Shaheen et al, 2016*).

SAFETY SUMMARY

Contraindications

- Hypersensitivity to any component of their formulations
- Patients receiving rilpivirine-containing products.

Warnings and precautions

- Acute interstitial nephritis, cyanocobalamin deficiency, *Clostridium difficile*-associated diarrhea, bone fractures, hypomagnesemia, and fundic gland polyps.
- Concomitant use with clopidogrel, St. John's Wort, rifampin, high-dose methotrexate, and some antiretroviral medications (eg, protease inhibitors such as atazanavir and nelfinavir) should be avoided.
- Co-administration of PPIs with warfarin may increase international normalized ratio (INR) and prothrombin time; the dose of warfarin may need to be adjusted. False positive results for diagnostic investigations of neuroendocrine tumors may occur due to an increase in serum chromogranin A (CgA) levels.
- Cutaneous and systemic lupus erythematosus have been reported in patients taking PPIs; new onset events and exacerbations of existing autoimmune disease have occurred.
- Symptomatic response to PPI therapy does not preclude the presence of gastric malignancy.

Adverse effects

- In general, the PPIs are well tolerated; abdominal pain, diarrhea, flatulence, headache, nausea, and vomiting are the most frequently reported adverse events (>2% adults).

- Long-term use of PPIs for 5 or more years has been associated with an increase in hip fractures (*Targownik et al, 2008; Islam et al, 2018; Poly et al, 2019*). When administered for 7 or more years, PPIs have been associated with a significantly increased risk of an osteoporosis-related fracture. At this time, there is inadequate evidence to mandate bone density studies and calcium supplementation in patients receiving chronic PPI therapy (*Freedberg et al, 2017; Kahrilas et al, 2008*). Additional data are needed to determine the value of osteoporotic medications in patients receiving long-term PPI therapy (*Targownik et al, 2008*). The 2013 guidelines for the diagnosis and management of GERD recommend continuation of PPI therapy unless additional risk factors for osteoporosis exist (*Katz et al, 2013*).
- The concomitant use of PPIs with thienopyridines such as clopidogrel was addressed in a consensus guideline from the American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association, which recommended PPI therapy be continued unless additional risk factors for cardiovascular disease exist (*Abraham et al, 2010*). A systematic review exploring the use of PPIs in combination with dual antiplatelet therapy that included clopidogrel showed inconclusive results for causing cardiovascular events while another systematic review showed an increase in cardiovascular events with PPIs in 1 analysis and only with pantoprazole, lansoprazole, and esomeprazole but not with omeprazole in another (*Malhotra et al, 2018; Melloni et al, 2015; Sherwood et al, 2015*). In a large, longitudinal, observational study of patients discharged after acute myocardial infarction treated with percutaneous coronary intervention, the use of clopidogrel or prasugrel in combination with a PPI was associated with statistically significantly more cardiovascular events than patients not discharged on a PPI (adjusted hazard ratio [HR], 1.38; 95% confidence interval [CI], 1.21 to 1.58). However, the authors noted that patients prescribed a concurrent PPI were more likely to be older and have more complex comorbidity profiles (*Jackson et al, 2016*). Two recent meta-analyses of randomized controlled trials (RCTs) and observational studies found that the combined use of thienopyridines (mainly clopidogrel) and PPIs led to increases in outcomes such as recurrence of myocardial infarction, stroke, and death; however, 1 of the meta-analyses separately analyzed the results from RCTs and observational studies and found no risk difference in the RCTs. Only the observational studies pointed to an increased risk of adverse outcomes with combined use (*Pang et al, 2019*; *Khan et al, 2019)*.
- Recent research has demonstrated an association with PPIs and cardiovascular, renal, and neurological morbidity. PPI use interferes with acid production in endothelial lysosomes, leading to oxidative stress and accelerated cell death, and may contribute to the pathogenesis of the aforementioned morbidities (*Yepuri et al, 2016*).
  - A retrospective study using a data mining strategy identified 2.9 million patients in the general population taking PPIs for GERD. Data showed that GERD patients exposed to PPIs had a 1.16-fold increased association with myocardial infarction and a 2-fold increased association with cardiovascular mortality. H_2-receptor antagonists used for GERD were not associated with an increased cardiovascular risk (*Shah et al, 2015*). Another retrospective study in Taiwan found that PPI use was associated with an increased risk of hospitalization for ischemic stroke (HR, 1.36; 95% CI, 1.14 to 1.620; p = 0.001) within the 120-day period after PPI initiation (*Wang et al, 2017*). A systematic review of 6 nonrandomized observational studies directly comparing the effect of PPI use on either mortality (3 studies), and/or examining the relationship of PPI use with myocardial infarct, stroke, or peripheral arterial event determined that PPI use was associated with a higher risk for all-cause mortality (odds ratio [OR], 1.68; 95% CI, 1.53 to 1.84) and major cardiovascular events (OR, 1.54; 95% CI, 1.11 to 2.13). The rate of major cardiovascular events was also significantly higher in patients taking PPIs (OR, 1.54; 95% CI, 1.11 to 2.13, p = 0.01) (*Shiraev et al, 2018*).
  - In a large cohort study, 144,032 incident users of either PPIs or H_2-antagonists were followed for 5 years. Patients using PPIs had an increased risk of incident chronic kidney disease (HR, 1.26; 95% CI, 1.2 to 1.33) and increased risk of estimated glomerular filtration rate decline and end-stage renal disease as compared to H_2-antagonist users (*Xie et al, 2017*). Similar patterns were identified in another large population-based cohort study; twice-daily PPI dosing was associated with a higher risk than once-daily dosing (*Lazarus et al, 2016*). A large retrospective analysis found that PPI users had an increased risk for doubled serum creatinine levels (HR, 1.26; 95% CI, 1.05 to 1.51) and an increased risk for 30% or more decrease in estimated glomerular filtration rate (HR, 1.26; 95% CI, 1.16 to 1.36) compared to H_2-antagonist users. The risks of end-stage renal disease (HR, 2.40; 95% CI, 0.76 to 7.58) and acute kidney injury (HR, 1.30; 95% CI, 1.00 to 1.69) were also elevated with PPIs, but the risk elevations were not statistically significant. The study concluded that PPIs are associated with the risk of chronic kidney disease progression (*Klatte et al, 2017*). A retrospective analysis of claims data in Taiwan also identified an increased risk for PPI-associated chronic kidney disease in PPI-users compared to non-users (*Hung et al, 2018*). Meta-analyses evaluating the risk of chronic kidney disease have identified an increased risk for chronic kidney disease and end-stage renal disease in PPI-users as compared to both H_2-receptor antagonists-users and non-PPI users (*Nochaiwong et al, 2018; Wijarnpreecha et al, 2017*). However, these findings are based on observational studies and were deemed as low-quality evidence by Nochaiwong et al.

A prospective cohort study using observational data from 73,679 patients ≥ 75 years and dementia-free at baseline were analyzed. Patients on PPIs (N = 2950) had a significantly increased risk of dementia than patients not on PPIs (HR, 1.44; 95% CI, 1.36 to 1.52, p < 0.001) (*Gomm et al, 2016*). However, this finding has not been consistently replicated. A prospective cohort study of 13,684 patients enrolled in the Nurses' Health Study II did not find a significant association between PPI use and cognitive function after adjusting for H_2-antagonist use and other confounding variables (*Lochhead et al, 2017*). Additionally, a nested case-control study using data from the Finnish nationwide healthcare registers did not find an association between PPI use and Alzheimer's disease (OR, 1.03; 95% CI, 1.00 to 1.05) (*Taipale et al, 2017*). A prospective study analyzing Denmark survey data did not find an association between PPI use and cognitive decline (adjusted cognitive difference of 0.69; 95% CI, -4.98 to 3.61) (*Wod et al, 2018*). A prospective population-based cohort study (N = 3484) found no association between PPI use and dementia risk (HR, 0.87, 95% CI, 0.65 to 1.18 for 1 year of daily use; HR, 0.99, 95% CI, 0.75 to 1.30 for 3 years of daily use; HR, 1.13, 95% CI, 0.82 to 1.56 for 5 years of daily use) *(Gray et al*, *2018*). An observational longitudinal study found PPIs were not associated with dementia or Alzheimer's disease. Patients on continuous and intermittent therapy had a lower risk of cognitive decline (HR, 0.78, 95% CI, 0.66 to 0.93 and HR, 0.84, 95% CI, 0.76 to 0.93, respectively) (*Goldstein et al*, *2017*). A recent meta-analysis evaluated 11 observational studies (N = 642,949) and found no association between PPI use and dementia risk (adjusted HR, 1.10; 95% CI, 0.88 to 1.37) *(Khan et al 2020).*

- A recent meta-analysis found an association between gastric mucosal atrophy and long-term PPI treatment. In this analysis of 13 studies (1465 patients on long-term PPI and 1603 controls), patients on long-term PPI therapy had higher rates of gastric atrophy (OR, 1.55; 95% CI, 1.00 to 2.41) than controls. A subgroup analysis noted that omeprazole and lansoprazole groups had higher rates of gastric atrophy compared to control groups, while esomeprazole had lower rates compared to control groups (*Li et al, 2017[bj]*). An increased risk of gastric cancer with long-term use of PPIs was also demonstrated in a recent meta-analysis; 2 studies (n = 17,158 patients) provided data for this outcome (*Islam et al, 2018*). Exposure to PPIs has also been linked with an increased risk for pancreatic cancer compared to unexposed patients (OR, 1.75; 95% CI, 1.12 to 2.72) in a meta-analysis that included both interventional and observational studies (*Alkhushaym et al 2020).*
- A meta-analysis of 7 studies (N=868,882) evaluating adverse events associated with long-term use of PPIs demonstrated an increased risk of community-acquired pneumonia (OR, 1.67; 95% CI, 1.04 to 2.67) for long-term users of PPIs, older patients (> 60 years) and those who took higher doses of PPIs.; (*Islam et al, 2018*).
- A recent large factorial, double-blind, randomized trial (N = 17,585) evaluated the effectiveness of pantoprazole for preventing upper gastrointestinal bleeding in patients receiving aspirin and/or rivaroxaban. The trial randomized patients into 3 different anticoagulation strategies, as well as 1:1 for pantoprazole or placebo for gastrointestinal prophylaxis. The primary safety composite endpoint of myocardial infarction, stroke, or cardiovascular death was not different between those receiving pantoprazole versus placebo (HR, 1.04; 95% CI, 0.93 to 1.15). Additionally, no significant difference in rates of other prespecified safety outcomes were detected, which included gastric atrophy, chronic kidney disease, dementia, and pneumonia; only enteric infections were more likely to occur in pantoprazole users (OR, 1.33; 95% CI, 1.01 to 1.75) *(Moayyedi et al 2019).*

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Dexlansoprazole	Delayed-release capsule	Oral	Treatment of symptomatic, non-erosive GERD (≥ 12 years of age): Once daily for 4 weeks Treatment of erosive esophagitis (≥ 12 years of age: Once daily for up to 8 weeks	Delayed-release capsules can be taken without regard to food. Delayed-release capsules can be opened and contents sprinkled onto applesauce for immediate consumption. Delayed-release capsules can be opened and contents mixed in 20 mL of water for administration in an oral syringe for immediate consumption. Refill the oral syringe with 10 mL of water twice to ensure all of the contents are

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Maintenance of healing of erosive esophagitis (≥ 12 years of age: Once daily for up to 6 months in adults and 16 weeks in patients 12 to 17 years of age	delivered. Delayed-release capsules can be opened with contents mixed in 20 mL of water and withdrawn in a catheter-tip syringe and administered by nasogastric tube. Refill the syringe with 10 mL of water twice to flush the tube.
Esomeprazole magnesium	Delayed-release capsules Delayed-release suspension (unit-dose packets) Delayed-release capsules (OTC) Delayed-release tablets (OTC)	Oral	Treatment of symptomatic GERD (≥ 12 years of age): Once daily for 4 to 8 weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: Once daily for 10 days Treatment of erosive esophagitis (≥ 12 years of age): Once daily for 4 to 16 weeks Maintenance of healing of erosive esophagitis: Once daily for up to 6 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Twice daily Risk reduction of NSAID-associated gastric ulcer: Once daily for up to 6 months Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	Should be taken at least 1 hour before meals. Capsules can be opened and contents sprinkled onto applesauce for immediate consumption. Contents can also be emptied into 60 mL catheter tipped syringe and shaken with 50 mL of water for administration via nasogastric tube. Packets for delayed-release suspension should be emptied into water (5 mL for 2.5 mg or 5 mg; 15 mL for 10 mg, 20 mg, or 40 mg), stirred, left for 2 to 3 minutes to thicken, and drank within 30 minutes. Can also be emptied into a catheter-tipped syringe for administration via nasogastric tube. Doses > 20 mg should not be exceeded in patients with severe liver impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Treatment of symptomatic GERD, short-term (1 to 11 years of age): Once daily for up to 8 weeks Treatment of erosive esophagitis (1 to 11 years of age): Once daily for 8 weeks (weight-based) Treatment of erosive esophagitis due to acid-mediated GERD (1 month to < 1 year of age): Once daily for up to 6 weeks (weight-based)	
Esomeprazole sodium	Powder for injection	IV	Treatment of symptomatic GERD with erosive esophagitis (Adults): once daily by IV injection or IV infusion for up to 10 days Risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults: IV infusion over 30 minutes followed by a continuous infusion over 3 days (72 hours) Treatment of symptomatic GERD with erosive esophagitis (1 month to 17 years of age): Once daily (weight-based) by IV infusion for up to 10 days	Should be discontinued in favor of oral therapy as soon as oral therapy is possible.
Lansoprazole	Delayed-release capsules	Oral	Treatment of symptomatic GERD	Should be taken before eating and swallowed whole.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	Delayed-release orally disintegrating tablets Delayed-release capsules (OTC) Delayed-release orally disintegrating tablets (OTC)		and heartburn (adults): Once daily for up to 8 weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: 2 to 3 times daily for 10 to 14 days Treatment of active duodenal ulcers: Once daily for 4 weeks Treatment of erosive esophagitis: Once daily for up to 16 weeks Treatment of active, benign gastric ulcer: Once daily for up to 8 weeks Healing of NSAID associated gastric ulcer: Once daily for 8 weeks Maintenance of healing duodenal ulcers: Once daily for up to 12 months Maintenance of healing of erosive esophagitis: Once daily for up to 12 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Once daily Risk reduction of NSAID-associated	Capsules (non-OTC) can be opened and contents sprinkled into applesauce, Ensure, pudding, cottage cheese, yogurt, or strained pears. May be mixed in 60 mL apple juice, orange juice, or tomato juice for immediate consumption. Contents can also be mixed into 40 mL apple juice for administration via nasogastric tube, flushing with additional juice. Orally disintegrating tablets should be placed on the tongue, allowed to disintegrate, and swallowed. Orally disintegrating tablets (non-OTC) may also be mixed with water (4 mL for 15 mg tablet or 10 mL for 10 mg tablet) in an oral syringe and gently shaken for oral or nasogastric tube administration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			gastric ulcer: Once daily up to 12 weeks Treatment of symptomatic GERD and erosive esophagitis (1 to 11 years of age): Once daily for up to 12 weeks (weight-based) Treatment of symptomatic nonerosive GERD (12 to 17 years of age): Once daily for up to 8 weeks Treatment of symptomatic GERD with erosive esophagitis (12 to 17 years of age): Once daily for up to 8 weeks Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	
Omeprazole magnesium	Delayed-release capsules Delayed-release suspension (unit-dose packets) Delayed-release tablets and orally disintegrating tablets (OTC)	Oral	Treatment of symptomatic GERD and heartburn (adults): Once daily for 4 weeks Treatment of symptomatic GERD and erosive esophagitis due to acid-mediated GERD (1 to 16 years of age): Once daily (weight-based) for up to 4 weeks for symptomatic GERD and for up to 12 weeks for erosive esophagitis due to acid-mediated GERD	Should be taken before eating. Capsules can be opened and contents sprinkled into applesauce for immediate consumption. Unit-dose packets should be emptied into water, stirred, left for 2 to 3 minutes to thicken, and drank within 30 minutes. Capsule contents and oral suspension can also be emptied into a catheter-tipped syringe for administration via nasogastric tube.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			H. pylori eradication to reduce the risk of duodenal ulcer recurrence (adults): Once or twice daily for 10 to 14 days; an additional 10 to 18 days of therapy may be needed Treatment of active duodenal ulcers (adults): Once daily for 4 weeks; some patients may require an additional 4 weeks Treatment of erosive esophagitis due to acid-mediated GERD (adults): Once daily for 4 to 16 weeks Treatment of erosive esophagitis due to acid-mediated GERD (1 month to < 1 year of age): Once daily for up to 6 weeks (weight-based) Treatment of active, benign gastric ulcer (adults): Once daily for 4 to 8 weeks Maintenance of healing of erosive esophagitis due to acid-mediated GERD (adults): Once daily for up to 12 months Maintenance of healing of erosive esophagitis due to acid-mediated GERD (1 to 16 years of age):	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Once daily (weight-based) for up to 12 months Note: Controlled studies do not extend beyond 12 months. Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome (adults): Once daily Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	
Omeprazole/ sodium bicarbonate	Capsules Powder for oral suspension (unit-dose packets): Capsules (OTC): Note: all formulations are indicated for adults only. Their safety and effectiveness in pediatric patients < 18 years of age have not been established.	Oral	Treatment of symptomatic GERD (with no esophageal erosions): Once daily for 4 to 8 weeks Treatment of active duodenal ulcers: Once daily for 4 weeks; some patients may require an additional 4 weeks Treatment of erosive esophagitis: Once daily for 4 to 16 weeks Treatment of active, benign gastric ulcer: Once daily for up to 12 months Maintenance of healing of erosive esophagitis: Once daily for up to 12 months Risk reduction of	Should be taken on an empty stomach at least 1 hour before a meal. Capsules should be swallowed intact with only water and should never be opened. Due to sodium bicarbonate content, one 40 mg unit (capsule or powder packet) is not equivalent to two 20 mg units; therefore, two 20 mg units should not be substituted for one 40 mg unit. Packets for delayed-release oral suspension should be emptied into a small cup with one to two tablespoons of water, stirred well, and drank immediately. Can also be constituted with 20 mL water in an appropriate-sized syringe for administration via nasogastric or orogastric tube. Patients receiving continuous nasogastric or orogastric tube feedings should have these feedings suspended 3 hours before and 1 hour after omeprazole/sodium bicarbonate administration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			upper gastrointestinal bleeding in critically ill patients: Once daily for up to 12 months Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	
Pantoprazole	Delayed-release suspension (unit-dose packets) Delayed-release tablets Powder for injection	Oral, IV	Treatment of erosive esophagitis associated with GERD: Delayed-release suspension, delayed-release tablet: Once daily for up to 8 to 16 weeks Powder for injection: Once daily for 7 to 10 days Maintenance of healing of erosive esophagitis: Delayed-release suspension, delayed-release tablet: 40 mg daily for up to 12 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Delayed-release suspension, delayed-release tablet: Twice daily Powder for injection: Twice daily Treatment of erosive esophagitis (≥ 5 years of age): Delayed-release	Powder for injection should be discontinued in favor of oral therapy as soon as oral therapy is possible. Tablets can be taken with or without food and should be swallowed whole. Delayed-release oral suspension should only be administered approximately 30 minutes prior to a meal in 1 teaspoonful of applesauce (eat within 10 minutes) or apple juice (drink immediately). Can also be mixed with 10 mL apple juice in a catheter-tipped 60 mL syringe for administration via nasogastric tube or gastrostomy tube. No refrigeration required. Can be reconstituted for 2-minute or 15-minute infusion.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			suspension, delayed-release tablet: Once daily for 8 weeks	
Rabeprazole	Delayed-release tablets Sprinkle delayed-release capsules	Oral	Treatment of symptomatic GERD: Once daily for up to 4 to 8 weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: Twice daily for 7 days Healing of duodenal ulcers: Once daily after the morning meal for up to 4 weeks Healing of erosive or ulcerative GERD: Once daily for 4 to 16 weeks Maintenance of healing of erosive or ulcerative GERD: Once daily for up to 12 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Once daily Treatment of symptomatic GERD in adolescent patients ≥ 12 years of age: Once daily for up to 8 weeks Treatment of GERD in pediatric patients 1 to 11 years of age (Aciphex Sprinkle): Once daily for up to 12 weeks (weight-based)	Take 30 minutes before a meal. For *H. pylori* regimen, take with morning and evening meals. Swallow tablets whole; do not chew, crush, or split. Contents of the Sprinkle capsules should be sprinkled on a spoonful of soft food or liquid, take the full dose within 15 minutes.

See the current prescribing information for full details

CONCLUSION

- PPIs are the most potent inhibitors of gastric acid secretion available.
- All of the PPIs are FDA-approved for the treatment and maintenance of GERD and, with the exception of dexlansoprazole and omeprazole with sodium bicarbonate, for the treatment of pathological hypersecretory conditions.
- With the exception of dexlansoprazole, esomeprazole sodium, omeprazole with sodium bicarbonate, and pantoprazole, all of the PPIs are approved for the eradication of *H. pylori* to reduce the risk of duodenal ulcer recurrence.
- Dexlansoprazole and omeprazole with sodium bicarbonate are the only PPIs that are not FDA-approved for use in young children. Dexlansoprazole is indicated in patients ≥ 12 years of age, while omeprazole with sodium bicarbonate is only indicated in adults.
- All orally administered PPIs are available in delayed-release oral formulations, with the exception of omeprazole with sodium bicarbonate. All oral products can be dosed once daily.
- Dexlansoprazole is uniquely formulated to release at different time intervals, at 2 different sites of the small intestine. The clinical significance of this is unknown.
- Esomeprazole magnesium, omeprazole magnesium, and pantoprazole are available as granules for a delayed-release oral suspension. Omeprazole with sodium bicarbonate is available as a powder for oral suspension. Rabeprazole is available in a sprinkle delayed-release capsule formulation. Lansoprazole and omeprazole magnesium are available as delayed-release orally disintegrating tablets.
- Esomeprazole magnesium, lansoprazole, omeprazole, omeprazole magnesium, and omeprazole with sodium bicarbonate are also available in OTC formulations.
- Esomeprazole sodium and pantoprazole are available in intravenous formulations for short-term use in patients unable to take medications by mouth.
- Rabeprazole, esomeprazole magnesium, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are all available generically, however, some formulations (eg, oral suspensions) remain available only as brands.
- Current medical evidence demonstrates that PPI therapy is highly effective in treating, providing symptomatic relief, and preventing relapse in gastric acid disorders such as erosive esophagitis and symptomatic GERD.
  - Meta-analyses and direct comparator trials have demonstrated that lansoprazole, omeprazole, pantoprazole, and rabeprazole have comparable healing rates, maintenance of healing, and symptomatic relief of GERD (*Bardhan et al, 2001; Caro et al, 2001; Edwards et al, 2001; Klok et al, 2003; Pace et al, 2005; Sharma et al, 2001*).
  - Richter et al reported statistically faster and greater symptomatic relief with lansoprazole compared to omeprazole; however, the significance of these differences in clinical practice is not known (*Richter et al, 2011[b]*).
  - There is evidence through meta-analyses and several clinical trials that esomeprazole provides higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole, and pantoprazole (*Castell et al, 2002; Devault et al, 2006; Edwards et al, 2001; Kahrilas et al, 2000; Klok et al, 2003; Labenz et al, 2005[a]; Labenz et al, 2005[b]; Richter et al, 2001[a]*).
  - Subgroup analyses in 2 trials noted better healing rates with esomeprazole in patients with more severe disease (*Labenz et al, 2005[a]; Schmitt et al, 2006*).
  - Evidence suggests that there is no major difference in efficacy among the various PPIs for the short-term management of reflux esophagitis when administered in equivalent dosages.
  - Currently, there is a lack of head-to-head studies of dexlansoprazole with the other agents in this class.
- Clinical studies have demonstrated that PPIs are also highly effective in the treatment of peptic ulcer disease caused by chronic NSAID therapy or *H. pylori* infection when coupled with antibiotics.
  - Meta-analyses and head-to-head trials comparing PPIs to each other have shown comparable rates of eradication when administered at comparable doses and paired with comparable antibiotic regimens.
  - Results of meta-analyses suggest that regimens containing the new generation PPIs (esomeprazole and rabeprazole) may be more effective than the other PPIs at eradicating *H. pylori* (*McNicholl et al, 2012; Xin et al, 2016*).
  - Additional studies are needed before definitive conclusions can be made regarding the use of certain PPIs in specific patient populations.
- PPIs are generally well tolerated; abdominal pain, diarrhea, flatulence, headache, nausea, and vomiting are the most frequently reported adverse events. However, PPIs have been associated with a number of potential safety concerns.

  - Warnings and precautions include interstitial nephritis, increased risk of *Clostridium difficile*-associated diarrhea, cyanocobalamin deficiency, hypomagnesemia, cutaneous and systemic lupus erythematosus, interactions with clopidogrel and St. John's Wort or rifampin, and increased risk of osteoporosis-related fractures with long-term use.
- Current consensus among various national and international treatment guidelines recommend a PPI as the first-line therapy in the treatment and maintenance of healed erosive esophagitis, symptomatic GERD, dyspepsia (patients ≤ 55 years and no alarm features), and peptic ulcer disease caused by NSAID therapy. Triple and quadruple combination therapy with antibiotics and a PPI are considered first-line therapy for peptic ulcer disease caused by *H. pylori*. Most treatment guidelines do not recommend one PPI over another, and no treatment guideline recommends one formulation of a PPI over another.

REFERENCES

- Abraham NS, Hlatky MA, Antman EM, et al; ACCF/ACG/AHA. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol*. 2010;56(24):2051-2066.
- ACIPHEX prescribing information. Eisai Inc. Woodcliff Lake, NJ. September 2019.
- ACIPHEX SPRINKLE prescribing information. Cerecor, Inc. Rockville, MD. June 2018.
- Alkhushaym N, Almutairi AR, Althagafi A, et al. Exposure to proton pump inhibitors and risk of pancreatic cancer: a meta-analysis. *Expert Opin Drug Saf*. 2020 Jan 21:1-8. doi: 10.1080/14740338.2020.1715939.
- American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology*. 2011 Mar;140(3):1084-91.
- Armstrong D, Talley NJ, Lauritsen K, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. *Aliment Pharmacol Ther*. 2004;20(4):413-21.
- Bardhan KD, Van Rensburg C. Comparable clinical efficacy and tolerability of 20 mg pantoprazole and 20 mg omeprazole in patients with grade I reflux esophagitis. *Aliment Pharmacol Ther*. 2001;15:1585-91.
- Bazzoli F, Pozzato P, Zagari M, et al. Efficacy of lansoprazole in eradicating Helicobacter pylori: a meta-analysis. *Helicobacter*. 1998;3(3):195-201.
- Bergsland E. Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma). UpToDate Web site. http://www.uptodate.com/contents/management-and-prognosis-of-the-zollinger-ellison-syndrome-gastrinoma?source=search_result&search=zollinger&selectedTitle=2%7E81. Updated October 21, 2019. Accessed January 29, 2020.
- Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared to omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. *Clin Ther*. 2001;23(7):998-1017.
- Castell D, Bagin R, Goldlust B, et al. Comparison of the effects of immediate-release omeprazole powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in patients with symptomatic gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2005;21(12):1467-74.
- Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared to lansoprazole (30 mg) in the treatment of erosive esophagitis. *Am J Gastroenterol*. 2002;97:575-83.
- Chan FKL, Lanas A, Scheiman J, et al. Celecoxib vs omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomized trial. *Lancet*. 2010;376:173-9.
- Chey W, Huang B. Jackson RL. Lansoprazole and esomeprazole in symptomatic GERD: a double-blind, randomized, multicentre trial in 3000 patients confirms comparable symptom relief. Oesophagitis. *Clin Drug Invest*. 2003;23(2):69-84.
- Chey WD, Leontiadis GI, Howden CW, et al. ACG Clinical Guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2017; 112:212-38.
- Choi HS, Park DI, Hwang SJ, et al. Double-dose, new-generation proton-pump inhibitors do not improve eradication rate. *Helicobacter*. 2007; 2(6):638-42.
- Clinical Pharmacology Web site. http://www.clinicalpharmacology.com. Accessed January 29, 2020.
- Conrad SA, Gabrielli A, Margolis B, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension vs intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. *Crit Care Med*. 2005;33(4):760-5.
- Dean L. PubMed Clinical Q&A [Internet]. Bethesda, MD. National Center for Biotechnology Information. Comparing Proton Pump Inhibitors. 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004954/. Accessed January 29, 2020.
- Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to omeprazole, 20 mg once daily, in the healing of erosive gastroesophageal reflux disease. *Scand J Gastroenterol*. 2000;35:1245-50.
- Devault KR, Johanson JF, Johnson DA, et al. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. *Clin Gastroenterol Hepatol*. 2006 Jul;4(7):852-9.
- DEXILANT prescribing information. Takeda Pharmaceuticals America, Inc. Deerfield, IL. June 2018.
- Drugs@FDA. U.S. Food and Drug Administration. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed January 29, 2020.
- Edwards SJ, Lind T, Lundell L. Systematic review of proton-pump inhibitors for the acute treatment of reflux oesophagitis. *Aliment Pharmacol Ther*. 2001;15(11):1729-36.
- Eichenwald EC. Diagnosis and management of gastroesophageal reflux in preterm infants. *Pediatrics*. 2018 Jul;142(1). doi: 10.1542/peds.2018-1061.
- Fass R, Chey WD, Zakko SF, et al. Clinical trial: the effect of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. *Aliment Pharmacol Ther*. 2009;29:1261-72.

- Fass R, Johnson DA, Orr WC, et al. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. *Am J Gastroenterol.* 2011 Mar;106(3):421-31.
- Fass R, Inadomi J, Han C, et al. Maintenance of heartburn relief after step-down from twice-daily proton pump inhibitor to once-daily dexlansoprazole modified release. *Clin Gastroenterol Hepatol.* 2012 Mar;10(3):247-53.
- Felga G, Silva FM, Barbuti RC, et al. Clarithromycin-based triple therapy for Helicobacter pylori treatment in peptic ulcer patients. *J Infect Dev Ctries*. 2010 Nov 24;4(11):712-6.
- Fennerty MB, Johanson JF, Hwang C, et al. Efficacy of esomeprazole 40 mg vs lansoprazole 30 mg for healing moderate-to-severe erosive oesophagitis. *Aliment Pharmacol Ther*. 2005;21(4):455-63.
- Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology*. 2017 Mar;152(4):706-15.
- Fujimoto K, Hongo M; Maintenance Study Group. Safety and efficacy of long-term maintenance therapy with oral dose of rabeprazole 10 mg once daily in Japanese patients with reflux esophagitis. *Intern Med*. 2011;50(3):179-88.
- Gisbert JP, Khorrami S, Calvet X, et al. Pantoprazole-based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis. Eur J *Gastroenterol Hepatol*. 2004(a);16(1):89-99.
- Gisbert JP, Khorrami S, Calvet X, et al. Systematic review: rabeprazole-based therapies in Helicobacter pylori eradication. *Aliment Pharmacol Ther*. 2003;17(6):751-64.
- Gisbert JP, Pajares JM. Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis. *Dig Liver Dis*. 2004(b);36(4)253-9.
- Goh KL, Benamouzig R, Sander P, et al; EMANCIPATE. Efficacy of pantoprazole 20 mg daily compared to esomeprazole 20 mg daily in the maintenance of healed gastroesophageal reflux disease: a randomized, double-blind comparative trial-the EMANCIPATE study. *Eur J Gastroenterol Hepatol*. 2007;19(3):205-11.
- Goldstein FC, Steenland K, Zhao L, et al. Proton pump inhibitors and risk of mild cognitive impairment and dementia. *J Am Geriatr Soc*. 2017 Sep;65(9):1969-1974. doi: 10.1111/jgs.14956.
- Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol*. 2016 Apr;73(4):410-6.
- Gray SL, Walker RL, Dublin S, et al. Proton pump inhibitor use and dementia risk: prospective population-based study. *J Am Geriatr Soc*. 2018;66(2):247-253. doi: 10.1111/jgs.15073.
- Haddad I, Kierkus J, Tron E, et al. Efficacy and safety of rabeprazole in children (1-11 years) with gastroesophageal reflux disease: a multicenter, double-blind, parallel-group study. *J Pediatr Gastroenterol Nutr*. 2013. 57(6):798-807. doi: 10.1097/MPG.0b013e3182a4e718
- Howden CW, Ballard EDI, Robieson W. Evidence for therapeutic equivalence of lansoprazole 30 mg and esomeprazole 40 mg in the treatment of erosive oesophagitis. *Clin Drug Invest*. 2002;22(2):99-109.
- Howden CW, Larsen LM, Perez MC, et al. Clinical trial: efficacy and safety of dexlansoprazole MR 60 mg and 90 mg in healed erosive oesophagitis – maintenance of healing and symptom relief. *Aliment Pharmacol Ther*. 2009;30:895-907.
- Hsu PI, Lai KH, Lin CK, et al. A prospective randomized trial of esomeprazole-vs pantoprazole-based triple therapy for Helicobacter pylori eradication. *Am J Gastroenterol*. 2005;100(11):2387-92.
- Hung SC, Liao FK, Hung HC, et al. Using proton pump inhibitors correlates with an increased risk of chronic kidney disease: a nationwide database-derived case-controlled study. *Fam Pract*. 2018;35(2):166-171. doi: 10.1093/fampra/cmx102.
- Islam MM, Poly TN, Walther BA, et al. Adverse outcomes of long-term use of proton-pump inhibitors: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* 2018;30(12):1395-1405. doi: 10.1097/MEG.0000000000001198.
- Jackson LR, Peterson ED, McCoy LA , et al. Impact of proton pump inhibitor use on the comparative effectiveness and safety of prasugrel versus clopidogrel: insights from the treatment with adenosine diphosphate receptor inhibitors: longitudinal assessment of treatment patterns and events after acute coronary syndrome (TRANSLATE-ACS) study. *J Am Heart Assoc*. 2016 Oct;5:e003824.
- Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN guidelines for the management of Helicobacter pylori in children and adolescents (update 2016). *J Pediatr Gastroenterol Nutr*. 2017 Jun;64(6):991-1003.
- Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared to omeprazole in reflux oesophagitis patients: a randomized controlled trial. *Aliment Pharmacol Ther*. 2000;14:1249-58.
- Kahrilas PJ, Shaheen NJ, Vaezi MF, et al; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology*. 2008 Oct;135(4):1383-91,1391.e1-5.
- Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013 Mar;108(3):308-28.
- Katz PO, Koch FK, Ballard ED, et al. Comparison of the effects of immediate-release omeprazole oral suspension, delayed-release lansoprazole capsules and delayed-release esomeprazole capsules on nocturnal gastric acidity after bedtime dosing in patients with nighttime GERD symptoms. *Aliment Pharmacol Ther*. 2007 Jan 15;25(2):197-205.
- Khan MA, Yuan Y, Iqbal U, et al. No association linking short-term proton pump inhibitor use to dementia: systematic review and meta-analysis of observational studies. *Am J Gastroenterol*. 2020 Jan 2. doi: 10.14309/ajg.0000000000000500. [Epub ahead of print]
- Khan SU, Lone AN, Asad ZUA, et al. Meta-analysis of efficacy and safety of proton pump inhibitors with dual antiplatelet therapy for coronary artery disease. *Cardiovasc Revasc Med*. 2019;20(12):1125-1133. doi: 10.1016/j.carrev.2019.02.002.
- Kinoshita Y, Ashida K, Hongo M; Japan. Rabeprazole Study Group for NERD. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. *Aliment Pharmacol Ther*. 2011 Jan;33(2):213-24.
- Klatte DCF, Gasparini A, Xu H, et al. Association between proton pump inhibitor use and risk of progression of chronic kidney disease. *Gastroenterology*. 2017;153(3):702-710. doi: 10.1053/j.gastro.2017.05.046.
- Klok RM, Postma MJ, van Hout BA, et al. Meta-analysis: comparing the efficacy of proton-pump inhibitors in short-term use. *Aliment Pharmacol Ther*. 2003;17(10):1237-45.
- Labenz J, Armstrong D, Lauritsen K, et al. A randomized comparative study of esomeprazole 40 mg vs pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. *Aliment Pharmacol Ther*. 2005[a];21(6):739-46.

- Labenz J, Armstrong D, Lauritsen K, et al. Esomeprazole 20 mg vs pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. *Aliment Pharmacol Ther*. 2005[b];22(9):803-11.
- Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol*. 2012 Mar;107(3):345-60.
- Laine L, Katz PO, Johnson DA, et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs. esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. *Aliment Pharmacol Ther*. 2011 Jan;33(2):203-12.
- Lansoprazole prescribing information. Cadila Healthcare Limited Ltd. Ahmedabad, India. June 2018.
- Lanza FL, Chan FKL, Quigley EMM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol. 2009*;104:728-38.
- Lauritsen K, Devière J, Bigard MA, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. *Aliment Pharmacol Ther*. 2003;17(3):333-41.
- Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016 Feb;176(2):238-46.
- Li MJ, Li Q, Sun M, Liu LQ. Comparative effectiveness and acceptability of the FDA-licensed proton pump inhibitors for erosive esophagitis: A PRISMA-compliant network meta-analysis. *Medicine (Baltimore*). 2017[a];96(39):e8120. doi: 10.1097/MD.0000000000008120.
- Li Z, Wu C, Li L, et al. Effect of long-term proton pump inhibitor administration on gastric mucosal atrophy: A meta-analysis. *Saudi J Gastroenterol*. 2017[b];23(4):222-228.
- Liang CM, Kuo MT, Hsu PI, et al. First-week clinical responses to dexlansoprazole 60 mg and esomeprazole 40 mg for the treatment of grades A and B gastroesophageal reflux disease. *World J Gastroenterol*. 2017;23(47):8395-8404. doi: 10.3748/wjg.v23.i47.8395.
- Lightdale CJ, Schmitt C, Hwang C, et al. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. *Dig Dis Sci*. 2006 May;51(5):852-7.
- Lochhead P, Hagan K, Joshi AD, et al. Association between proton pump inhibitor use and cognitive function in women. *Gastroenterology*. 2017;153(4):971-979. doi: 10.1053/j.gastro.2017.06.061.
- Malfertheiner P, Megraud F, O'Morain CA, et al.; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection—the Maastricht V/ Florence Consensus Report. *Gut*. 2017;66(1):6-30. doi: 10.1136/gutjnl-2016-312288.
- Malhotra K, Katsanos AH, Bilal M, et al. Cerebrovascular outcomes with proton pump inhibitors and thienopyridines: a systematic review and meta-analysis. *Stroke*. 2018 Feb;49(2):312-318. doi: 10.1161/STROKEAHA.117.019166.
- McNicholl AG, Linares PM, Nyssen OP, et al. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther.* 2012 Sep;36(5):414-25.
- Melloni C, Washam JB, Jones WS, et al. Conflicting results between randomized trials and observational studies on the impact of proton pump inhibitors on cardiovascular events when coadministered with dual antiplatelet therapy. *Circ Cardiovasc Qual Outcomes*. 2015;8:47-55.
- Metz DC, Howden CW, Perez MC, et al. Clinical trial dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive esophagitis. *Aliment Pharmacol Ther*. 2009;29:742-54.
- Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology*. 2019 Sep;157(3):682-691.e2. doi: 10.1053/j.gastro.2019.05.056.
- Moayyedi PM, Lacy BE, Andrews CN, et al. ACG and CAG clinical guideline: management of dyspepsia. *Am J Gastroenterol*. 2017 Jul;112(7):988-1013.
- Mönnikes H, Schwan T, van Rensburg C, et al. Randomised clinical trial: sustained response to PPI treatment of symptoms resembling functional dyspepsia and irritable bowel syndrome in patients suffering from an overlap with erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2012 Jun;35(11):1279-89.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Zollinger-Ellison syndrome. Available at: https://www.niddk.nih.gov/health-information/digestive-diseases/zollinger-ellison-syndrome. Accessed January 29, 2020.
- NEXIUM prescribing information. AstraZeneca LP. Wilmington, DE. June 2018.
- NEXIUM IV prescribing information. AstraZeneca LP. Wilmington, DE. September 2019.
- NEXIUM 24HR capsules prescribing information. Pfizer Consumer Healthcare. Madison, NJ. April 2019.
- NEXIUM 24HR tablets prescribing information. Pfizer Consumer Healthcare. Madison, NJ. April 2019.
- Nochaiwong S, Ruengorn C, Awiphan R, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2018 Feb 1;33(2):331-342. doi: 10.1093/ndt/gfw470.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research. Available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed January 29, 2020.
- Pace F, Annese V, Prada A, et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomized, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. *Dig Liver Dis*. 2005;37:741-50.
- Pang J, Wu Q, Zhang Z, et al. Efficacy and safety of clopidogrel only vs. clopidogrel added proton pump inhibitors in the treatment of patients with coronary heart disease after percutaneous coronary intervention: A systematic review and meta-analysis. *Int J Cardiol Heart Vasc*. 2019;23:100317. doi: 10.1016/j.ijcha.2018.12.016.
- Pilotto A, Franceschi M, Leandro G, et al. Comparison of four proton-pump inhibitors for the short-term treatment of esophagitis in elderly patients. *World J Gastroenterol*. 2007;13(33):4467-72.
- Poly TN, Islam MM, Yang HC, Wu CC, Li YJ. Proton pump inhibitors and risk of hip fracture: a meta-analysis of observational studies. *Osteoporos Int*. 2019;30(1):103-114. doi: 10.1007/s00198-018-4788-y.
- Pouchain D, Bigard MA, Liard F, et al. Gaviscon® vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. a direct comparative randomised trial. *BMC Gastroenterol*. 2012 Feb 23;12:18.
- PREVACID prescribing information. Takeda Pharmaceuticals America, Inc. Deerfield, IL. June 2018.
- PREVACID 24HR prescribing information. GlaxoSmithKline Consumer Healthcare Holdings, LLC. Warren, NJ. April 2019.
- PRILOSEC suspension prescribing information. Covis Pharma. Zug, 6300 Switzerland. August 2018.
- PRILOSEC OTC product information. Procter and Gamble. Cincinnati, OH. April 2019.

- PROTONIX prescribing information. Wyeth Pharmaceuticals Inc. Philadelphia, PA. April 2019.
- PROTONIX IV prescribing information. Wyeth Pharmaceuticals Inc. Philadelphia, PA. April 2019.
- Ramdani A, Mignon M, Samoyeau R. Effect of pantoprazole vs other proton-pump inhibitors on 24-hour intragastric pH and basal acid output in Zollinger-Ellison syndrome. *Gastroenterol Clin Biol*. 2002;26(4):355-9.
- Regula J, Butruk E, Dekkers CP, et al. Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole vs omeprazole. *Am J Gastroenterol*. 2006 Aug;101(8):1747-55.
- Richter JE, Kahrilas PJ, Johanson J, et al. Efficacy and safety of esomeprazole compared to omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *Am J Gastroenterol*. 2001[a];96:656-65.
- Richter JE, Kahrilas PJ, Sontag SJ, et al. Comparing lansoprazole and omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients. *Am J Gastroenterol*. 2001[b];96:3089-98.
- Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr*. 2018;66(3):516-554. doi: 10.1097/MPG.0000000000001889.
- Scheiman JM, Devereaux PJ, Herlitz J, et al. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). *Heart*. 2011 May;97(10):797-802.
- Schmitt C, Lightdale CJ, Hwang C, et al. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. *Dig Dis Sci*. 2006 May;51(5):844-50.
- Scholten T, Gatz G, Hole U. Once-daily pantoprazole 40 mg and esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. *Aliment Pharmacol Ther*. 2003;18(6):587-94.
- Shah NH, Lependu P, Bauer-Mehren A, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PLoS ONE*. 10(6):e0124653.
- Shaheen NJ, Falk GW, Iyer PG, Gerson L. ACG clinical guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol*. 2016;111(1):30-50.
- Sharma VK, Leontiadis GI, Howden CW. Meta-analysis of randomized controlled trials comparing standard clinical doses of omeprazole and lansoprazole in erosive oesophagitis. *Aliment Pharmacol Ther*. 2001;15(2):227-31.
- Sharma P, Shaheen NJ, Perez MC, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation – results from two randomized controlled studies. *Aliment Pharmacol Ther*. 2009;29:731-41.
- Sherwood MW, Melloni C, Jones WS, et al. Individual proton pump inhibitors and outcomes in patients with coronary artery disease on dual antiplatelet therapy: a systematic review. *J Am Heart Assoc*. 2015;4(11):1-8.
- Shiraev TP, Bullen A. Proton pump inhibitors and cardiovascular events: a systematic review. *Heart Lung Circ*. 2018;27(4):443-450. doi: 10.1016/j.hlc.2017.10.020.
- Sugano K, Matsumoto Y, Itabashi T, et al. Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. *J Gastroenterol*. 2011 Jun;46(6):724-35.
- Taipale H, Tolppanen AM, Tiihonon M, et al. No association between proton pump inhibitor use and risk of Alzheimer's disease. *Am J Gastroenterol*. 2017;112(12):1802-1808. doi: 10.1038/ajg.2017.196.
- Targownik LE, Lix LM, Metge CJ, et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ. 2008 Aug;179(4):319-26.
- Tsai HH, Chapman R, Shepherd A, et al. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastro-oesophageal reflux patients: the COMMAND Study. *Aliment Pharmacol Ther*. 2004;20:657-65.
- Ulmer HJ, Beckerling A, Gatz G. Recent use of proton-pump inhibitor-based triple therapies for the eradication of H pylori: a broad data review. *Helicobacter*. 2003;8(2):95-104.
- van Pinxteren B, Sigterman KE, Bonis P, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev*. 2010 Nov 10;(11):CD002095.
- Vergara M, Vallve M, Gisbert JP, et al. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. *Aliment Pharmacol Ther*. 2003;18:647-54.
- Wang X, Fang JY, Lu R, et al. A meta-analysis: comparison of esomeprazole and other proton-pump inhibitors in eradicating Helicobacter pylori. *Digestion*. 2006;73(2-3):178-86.
- Wang YF, Chen YT, Luo JC, et al. Proton-pump inhibitor use and the risk of first-time ischemic stroke in the general population: a nationwide population-based study. Am J Gastroenterol. 2017 Jul;112(7):1084-1093.
- Welage LS. Pharmacologic features of proton-pump inhibitors and their potential relevance to clinical practice. *Gastroenterol Clin North Am*. 2003;32(3 Suppl):S25-35.
- Wijarnpreecha K, Thongprayoon C, Chesdachai S, et al. Associations of proton-pump inhibitors and H2 receptor antagonists with chronic kidney disease: a meta-analysis. *Dig Dis Sci*. 2017 Oct;62(10):2821-2827. doi: 10.1007/s10620-017-4725-5.
- Wod M, Hallas J, Andersen K, et al. Lack of association between proton pump inhibitor use and cognitive decline. *Clin Gastroenterol Hepatol*. 2018;16(5):681-689. doi: 10.1016/j.cgh.2018.01.034.
- Wolfe MM. Proton pump inhibitors: overview of use and adverse effects in the treatment of acid-related disorders. UpToDate Web site. http://www.uptodate.com/contents/overview-and-comparison-of-the-proton-pump-inhibitors-for-the-treatment-of-acid-related-disorders?source=search_result&search=proton+pump+inhibitors&selectedTitle=1%7E150. Updated January 7, 2020. Accessed January 29, 2020.
- Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology. 2000;118(2 Suppl 1):S9-31.
- Wu IC, Wu DC, Hsu PI, et al. Rabeprazole- vs esomeprazole-based eradication regimens for H pylori infection. Helicobacter. 2007;12(6):633-7.
- Xie Y, Bowe B, Li, T, et al. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. *Kidney Int*. 2017;91(6):1482-1494. doi: 10.1016/j.kint.2016.12.021
- Xin Y, Manson J, Govan L. Pharmacological regimens for eradication of Helicobacter pylori: an overview of systematic reviews and network meta-analysis. *BMC Gastroenterol*. 2016 Jul; 16(1):80.

- Yepuri G, Sukhovershin R, Nazari-Shafti TZ, et al. Proton pump inhibitors accelerate endothelial senescence. *Circ Res*. 2016 Jun;118(12):e36-42.
- ZEGERID prescribing information. Santarus, Inc. San Diego, CA. September 2019.
- ZEGERID OTC prescribing information. Bayer Healthcare LLC. Whippany, NJ. January 2019.

Publication Date: February 19, 2020