Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

Single-Ingredient Oral Proton Pump Inhibitors

Dexlansoprazole (*Dexilant*)

Esomeprazole (*Nexium, Generics*)

Lansoprazole (*Prevacid, Generics; Prevacid Solu Tab*)

Omeprazole (*Prilosec, Generics*)

Pantoprazole (*Protonix, Generics*)

Rabeprazole (*Aciphex, Generics; Aciphex Sprinkle*)

AHFS Classification: 56.28.36 Proton Pump Inhibitors

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Executive Summary

Proton pump inhibitors (PPIs) reduce gastric acid secretion and are employed for the management of gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD). They are useful for the treatment and prevention of gastroduodenal ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs), and among treatment regimens for the eradication of *Helicobacter pylori* (*H. pylori*).

Gastroesophageal reflux disease refers to a family of conditions caused by excessive reflux of digestive enzymes from the stomach. Disease subtypes, descriptive of the presence of erosions seen upon endoscopic examination, include non-erosive GERD (NERD), and erosive esophagitis (EE). Heartburn, regurgitation, and dysphagia are common GERD symptoms. Peptic ulcer disease is characterized by symptoms of epigastric tenderness, and burning pain exacerbated by fasting. Ulcers, which may occur in the stomach and duodenum, are damaged mucosal areas with active inflammation. The majority of peptic ulcers are attributed to *H. pylori* and NSAID-induced mucosal damage.

There are 6 main PPI agents available in the US including dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole— available in a variety of oral formulations. In the 2013 American College of Gastroenterology (ACG) guideline, authors concluded that PPIs are similarly efficacious for the relief of GERD symptoms and for the healing of erosive esophagitis. The 2017 ACG guideline for the management of *H.pylori* recommends PPIs among *H.pylori* eradication regimens, without specifying a preference since there was insufficient evidence comparing PPIs among modern treatment regimens. Moreover, guidelines do not prefer one agent over another when used for the prevention of NSAID-induced ulcers.

We performed a comprehensive literature search to identify systematic reviews (SRs) of randomized-controlled-trials (RCTs) with head-to-head comparisons of PPIs for the effectiveness of GERD and PUD- related outcomes. A high-quality SR was identified, published by the Oregon Evidence-Based Practice Centers group in 2009. More recent systematic reviews were then selected to supplement this information. Direct comparative evidence was extracted from 12 SRs to describe the treatment-effect differences between PPIs; 3 additional SRs were included for the safety discussion.

PPI Comparative Efficacy

Healing and Symptom Relief of Erosive Esophagitis and Non-erosive Esophagitis GERD

There were a few differences consistent among the identified SRs with respect to **esomeprazole compared** to **omeprazole** 20mg/day or **lansoprazole** 15 mg/day. Findings were in favor of esomeprazole when used at particular doses for certain outcomes: (1) when esomeprazole 40 mg/day was compared to omeprazole 20 mg/day for the healing of EE at week 4 and 8; (2) when esomeprazole 40 mg/day was compared to omeprazole 20 mg/day for EE-symptom resolution at week 4; and (3) when esomeprazole 20 mg/day was compared to lansoprazole 15 mg/day for prevention of EE relapse at 6 months. However, there was inconsistent SR evidence when esomeprazole was used at the lower 20 mg daily dose when compared to omeprazole 20 mg/day for the healing of EE at week 4 and 8.

There were no significant differences between esomeprazole compared to omeprazole or lansoprazole for the following outcomes: (1) esomeprazole 20 mg/daily versus omeprazole 20 mg/daily for the resolution of heartburn symptoms at week 4 in patients with erosive GERD; (2) esomeprazole 40 mg/daily versus lansoprazole 30 mg/daily for the week 8 healing rate of EE (Los Angeles grades A-D), or for GERD-symptom resolution at week 4; and (3) esomeprazole 20 or 40 mg/day versus omeprazole 20 mg/day for the resolution of heartburn symptoms at week 4 in patients with non-erosive GERD.

Comparing **esomeprazole** 40 mg/day **versus pantoprazole** 40 mg/day, no differences in the EE-healing rate at week 8, or GERD symptom relief in patients with EE or non-erosive esophagitis were found.

Regarding **dexlansoprazole,** no efficacy differences were reported between any other PPI at FDA-approved doses.

Regarding **rabeprazole** comparisons, there is consistent SR evidence showing no difference in the 8 week EE-healing rate between omeprazole 20 mg/daily and rabeprazole 10 or 20 mg/daily treatments. Concerning the prevention of EE-relapse at week 52, the effects of omeprazole 20 mg/daily versus rabeprazole 10 or 20 mg/daily also appear similar. One SR meta-analysis found a significant difference in favor of rabeprazole 20 mg/daily compared to omeprazole 20 mg/daily for the outcome of GERD-related symptom resolution. No differences were found between other rabeprazole-PPI comparisons.

Peptic Ulcer Related Outcomes

There were no differences between PPIs for the week 4 healing rate of duodenal ulcers, or for the prevention of NSAID-induced ulcers. Our findings are congruent with the 2017 ACG guideline for the management of *H.pylori*, as there was no SR evidence identified that compared the effect difference between individual PPIs while incorporated into modern treatment regimens for the eradication of *H.pylori*.

PPI Safety Profile

Long-term use of PPIs has been associated with a higher incidence of community and hospital acquired *Clostridium difficile*, and the development of hip fractures in older women. Other potential adverse effects include hypergastrinemia, vitamin B12 deficiency, magnesium deficiency, and decreased calcium and iron absorption. Professional prescribing information for each PPI warns about potential drug interactions with antiretrovirals, digoxin, agents dependent on gastric pH for absorption, methotrexate, tacrolimus, warfarin, and strong CYP2C19 or CYP3A4 inducers and inhibitors.

Five SRs included direct comparisons with respect to PPI tolerability; most of these are regarding esomeprazole comparisons. For the treatment of GERD, the adverse events related to esomeprazole are comparable to those involved with lansoprazole, pantoprazole, and omeprazole, based on 3 SRs. One SR meta-analysis compared rabeprazole to omeprazole for GERD maintenance therapy, with trials lasting as long as 8 weeks, and concluded no significant difference in adverse events. The 2009 SR by McDonagh et al is consistent with the findings

above as the authors conclude no significant differences between any particular PPI comparison based on short-term and long-term studies available.

Overall, there were a few differences found in favor of esomeprazole compared to omeprazole and lansoprazole for some, but not all, GERD-related endpoints at specific dosing; however, no differences were found for PUD-related outcomes. One SR meta-analysis found a significant difference in favor of rabeprazole 20 mg/daily compared to omeprazole 20 mg/daily only for GERD-related symptom resolution; yet, there were no differences for outcomes pertaining to the healing of erosive esophagitis, prevention of EE-relapse, or PUD-related endpoints.

Introduction

Proton pump inhibitors (PPIs) reduce gastric acid secretion. They are widely used to manage gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD), including but not limited to erosive esophagitis, Zollinger-Ellison syndrome, and gastric/duodenal ulcers. They are also useful for the prevention of gastroduodenal ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs), and among treatment regimens for the eradication of *Helicobacter pylori* (H. pylori).

There are 6 main PPI agents available in the United States (US) including dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. These are available in various salt forms and oral-delivery formulations. Over-the-counter PPI availability includes preparations with esomeprazole, lansoprazole, or omeprazole.

While all PPIs have FDA approval for GERD-related indications, only 3 have approval for the management of certain peptic ulcers (lansoprazole, omeprazole, and rabeprazole). Two PPIs have FDA approval for the prevention of NSAID-associated ulcers (esomeprazole and lansoprazole) and all PPIs except dexlansoprazole and pantoprazole are approved for *H.pylori* eradication. **Table 1** details the specific formulations, indications, and dosing for the single-ingredient PPI products currently available in the US. Table 1 of **Appendix A** provides a shorter summary table comparing the approved indications for these products.

This report will discuss the head-to-head comparative evidence available for single-ingredient oral PPI products used within FDA-approved dosing as listed in Table 1. The Utah Medicaid Preferred Drug List currently classifies the following agents as preferred: Dexilant (dexlansoprazole), Nexium (esomeprazole) capsules, Protonix (pantoprazole) suspension packets for patients under 12 years old, generic omeprazole 20 mg and 40 mg capsules, and generic pantoprazole.

Table 1. Single-Ingredient Oral Proton Pump Inhibitor Products[1]

Generic Name	Brand Name, Formulations	Indication and Dosage[a]
Dexlansoprazole[2]	**Dexilant** • DR capsule: 30 mg, 60 mg	**Treatment of Gastroesophageal Reflux Disease for Patients 12 years of age and older** A) **Healing of Erosive Esophagitis:** for all grades of EE, used up to 8 weeks, in patients 12 years of age and older • Dose: 60 mg once daily for up to 8 weeks B) **Maintenance of Healed Erosive Esophagitis and Relief of Heartburn:** for use up to 6 months in adults and 16 weeks in patients 12 to 17 years of age • Dose: 30 mg once daily C) **Treatment of Symptomatic Non-Erosive Gastroesophageal Reflux Disease:** for heartburn associated with symptomatic non-erosive GERD, used up to 4 weeks, in patients 12 and older • Dose: 30 mg once daily for up to 4 weeks May be taken without regard to meals

Table 1. Single-Ingredient Oral Proton Pump Inhibitor Products[1]

Generic Name	Brand Name, Formulations	Indication and Dosage[a]
Esomeprazole magnesium[3]	**Esomeprazole magnesium** **Nexium** • DR capsules: 20 mg, 40 mg; generics and OTC (20 mg) available • OTC DR tablet: 20 mg • Granules for oral suspension: 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg per packet	**Treatment of Gastroesophageal Reflux Disease** A) **Healing of Erosive Esophagitis:** for the short-term treatment (4 to 8 weeks) in the healing and symptomatic relief of diagnostically confirmed EE. For those not healed after 4 to 8 weeks, an additional 4 to 8 week course may be considered**.** Infants 1 month to less than 1 year, can be treated for up to 6 weeks. • Patients > 12 years: 20 to 40 mg once daily for 4-8 weeks • 12-17 year olds: 20 to 40 mg once daily for 4-8 weeks • 1-11 year olds: 10 mg for weight <20 kg; or 10 to 20 mg for weight > 20 kg once daily up to 8 weeks • 1 month to <1 year old: 2.5 mg daily for weight 3kg to 5kg; 5 to 10 mg daily for weight 5 kg to 7.5 kg; and 10 mg daily for weight 7.5 to 12 kg: B) **Maintenance of Healing of Erosive Esophagitis in Adults:** studies do not extend beyond 6 months • Adult Dose: 20 mg once daily C) **Symptomatic Gastroesophageal Reflux Disease:** for short-term treatment (4 to 8 weeks) of heartburn and other GERD symptoms for use in adults and children 1 year or older. • Patients >12 years old: 20 mg once daily for 4 weeks • Patients 1 to 11 years old: 20 mg once daily for up to 8 weeks **Risk Reduction of NSAID-Associated Gastric Ulcer:** patients are considered to be at risk due to their age (≥ 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months. • 20 to 40 mg once daily for up to 6 months **H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence:** indicated in combination with amoxicillin/clarithromycin to eradicate H. pylori for patients with duodenal ulcer disease (active or history of within the past 5 years). **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome:** for the long-term treatment of hypersecretory conditions • 40 mg twice daily Must be taken at least one hour before a meal
Esomeprazole strontium[4]	DR generic capsule: 49.3 mg—equivalent to 40 mg of esomeprazole Note: the 24.65 mg product has been discontinued[1]	**Treatment of Gastroesophageal Reflux Disease in Adults** A) **Healing of Erosive Esophagitis:** for short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed EE. For those who have not healed after 4 to 8 weeks of treatment, an additional course may be considered**.** • Adult dose: 24.65 to 49.3 mg once daily for 4-8 weeks B) **Maintenance of Healing of Erosive Esophagitis:** studies were 6 months duration • Adult Dose: 24.65 mg once daily C) **Symptomatic Gastroesophageal Reflux Disease:** for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD • Adult dose: 24.65 mg once daily for 4 weeks **Risk Reduction of NSAID-Associated Gastric Ulcer in Adults:** patients are considered to be at risk due to their age (≥ 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months • Adult dose: 24.65 to 49.3 mg once daily for up to 6 months **H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults:** indicated in combination with amoxicillin/clarithromycin to eradicate H. pylori in patients with duodenal ulcer disease (active or history of within the past 5 years). **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults:** for the long-term treatment of pathological hypersecretory conditions • Adult dose: 49.3 mg twice daily Must be taken at least one hour before a meal

Table 1. Single-Ingredient Oral Proton Pump Inhibitor Products[1]

Generic Name	Brand Name, Formulations	Indication and Dosage[a]
Lansoprazole[5]	**Prevacid** • DR Capsules: 15mg, 30 mg; generics and OTC (15 mg) available • Oral disintegrating tablet (Solutab): 15 mg, 30 mg First-Lansoprazole compounding kit: powder for suspension: 3 mg/mL (300 mL)	**Treatment of Gastroesophageal Reflux Disease** A) **Healing of Erosive Esophagitis in Patients 1 year of age and older:** for all grades of EE in adults and pediatric patients 12 years and older for short-term treatment (up to 8 weeks). Pediatric patients 1 year to 11 years of age can be treated up to 12 weeks. For adults who have not healed after 8 weeks of treatment, an additional 8 week course may be considered**.** • Patients ≥12 years old: 30 mg once daily • Patients 1 to 11 years of age: 15 to 30 mg per day based on weight B) **Maintenance of Healing of Erosive Esophagitis in Adults:** studies do not extend beyond 12 months • Adult dose: 15 mg once daily C) **Symptomatic Gastroesophageal Reflux Disease in Patients 1 year of age and older:** for short-term treatment (up to 8 weeks) of heartburn and other GERD symptoms in adults and children 1 year or older. • Patients ≥ 12 years old: 15 mg once daily • Patients 1 to 11 years of age: 15 to 30 mg per day based on weight **Treatment of Active Benign Gastric Ulcer in Adults:** for short-term treatment (up to 8 weeks) in adults for healing and symptom relief of active benign gastric ulcer • Adult dose: 30 mg once daily **Risk Reduction and Healing of NSAID-Associated Gastric Ulcer in Adults:** (1) for adults requiring continuous NSAID therapy with documented history of gastric ulcers; controlled studies did not extend beyond 12 weeks; and (2) for healing of NSAID-related gastric ulcers in adults who continue NSAID use; controlled studies for healing did not extend beyond 8 weeks • For healing: 30 mg once daily; For risk reduction: 15 mg once daily **Treatment of Active Duodenal Ulcer and for the Maintenance of Healed Duodenal Ulcers in Adults:** for short-term treatment (up to 4 weeks) in adults for healing and symptom relief of active duodenal ulcer; and for the maintenance of healed duodenal ulcers (controlled studies don't extend beyond 12 months). • Adult dose for treatment and maintenance: 15 mg once daily **H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults:** indicated in combination with amoxicillin/ clarithromycin to eradicate H. pylori for adults with duodenal ulcer disease (active or 1 year history of duodenal ulcer). Also indicated in dual therapy for those with clarithromycin intolerance or resistance. **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults:** for the long-term treatment of pathological hypersecretory conditions • 60 mg once daily Lansoprazole dosage forms must be taken before a meal

Table 1. Single-Ingredient Oral Proton Pump Inhibitor Products[1]

Generic Name	Brand Name, Formulations	Indication and Dosage[a]
Omeprazole[6]	**Omeprazole** Generics for Prilosec [DSC] • DR capsules: 10 mg, 20 mg, 40 mg • OTC DR 20 mg tablet and 20 mg orally-disintegrating tablet • First Omeprazole Powder for Suspension: 2 mg/ mL **Omeprazole magnesium** **Prilosec** • Granules for oral suspension: 2.5 mg, 10 mg packets • OTC DR capsules: 20.6 mg	**Treatment of Gastroesophageal Reflux Disease:** • Dosed as 20 mg once daily for adults; pediatric dosing is 2.5 mg to 20 mg daily per weight A) **Treatment of Erosive Esophagitis due to GERD in Adults and Children ≥ 1 month of age:** for short-term treatment of EE diagnosed by endoscopy. Patients 1 year and older should be treated for up to 8 weeks and can use an additional 4 weeks of treatment with inadequate response. Pediatric patients 1 month to less than 1 year should be treated up to 6 weeks. B) **Maintenance of Healing of Erosive Esophagitis to due GERD in Adults and Children ≥ 1 year of age:** controlled studies were up to 12 months C) **Symptomatic GERD in Adults and Children ≥1 year old:** for the treatment of heartburn and other GERD symptoms for up to 4 weeks **Treatment of Active Benign Gastric Ulcer in Adults:** for short-term treatment (4 to 8 weeks) of active benign gastric ulcer • Dosed as 40 mg once daily **Treatment of Active Duodenal Ulcer in Adults:** for short-term (up to four weeks) treatment of active duodenal ulcers. Most patients heal within four weeks, but some may require an addition 4 weeks of therapy. • Dosed as 20 mg once daily **H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults: (a)** indicated in triple therapy with clarithromycin/amoxicillin, to eradicate *H. pylori* in adults (with active or up to 1-year history of *H.pylori*); **(b)** in dual therapy with clarithromycin for treatment of adults with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori* **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults:** for the long-term treatment of pathological hypersecretory conditions • Initiate at 60 mg once daily and then adjusted to patient's needs [expected max daily of 360 mg in divided doses] Omeprazole dosage forms must be taken before a meal.
Pantoprazole sodium[7]	**Protonix** • DR tablet: 20 mg, 40 mg; generics available • Granules for oral suspension: 40 mg packet	**Treatment of Gastroesophageal Reflux Disease:** • Dosed as 40 mg once daily for adults and children ≥40 kg; Children 15 to 40 kg use 20 mg once daily dosing A) **Healing of Erosive Esophagitis in Adults and Pediatric Patients ≥5 years old**: for short-term use (up to 8 weeks) in the healing and symptomatic relief of EE. For adult patients who have not healed after 8 weeks, an additional 8-week course can be considered B) **Maintenance of Healing of Erosive Esophagitis in Adults Only:** for maintenance of healing of EE and reduction in relapse rates of daytime and nighttime heartburn symptoms in adult patients with GERD. Controlled studies did not extend beyond 12 months C) **Symptomatic Relief of EE associated with GERD in Adults and Pediatric Patients ≥5 years old:** for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of EE. **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults:** for the long-term treatment of pathological hypersecretory conditions • Dosed as 40 mg twice daily Take DR tables whole with or without food. Oral suspension preparations must be taken 30 minutes prior to a meal

Table 1. Single-Ingredient Oral Proton Pump Inhibitor Products[1]

Generic Name	Brand Name, Formulations	Indication and Dosage[a]
Rabeprazole sodium[8,9]	**Aciphex Tablet DR** • DR tablet: 20 mg; generic available	**Treatment of Gastroesophageal Reflux Disease** • Dosed as 20 mg once daily A) **Healing of Erosive or Ulcerative GERD in Adults:** for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative GERD. For patients who have not healed after 8 weeks of treatment, an additional 8-week course may be considered B) **Maintenance of Healing of Erosive or Ulcerative GERD in Adults:** for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative GERD. Controlled studies were up to 12 months C) **Symptomatic GERD in Adults and Adolescents ≥12 years old:** for the treatment of daytime and nighttime heartburn and other GERD symptoms in adults for up to 4 weeks. Also indicated for adolescents 12 years of age and above for up to 8 weeks **Treatment of Active Duodenal Ulcer in Adults:** for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks • Dosed as 20 mg once daily after the morning meal **H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults:** indicated in combination with amoxicillin/clarithromycin to eradicate H.pylori in adults with duodenal ulcer disease (active or history within the past 5 years). • Dosed as 20 mg twice daily with morning and evening meals **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults:** for the long-term treatment of pathological hypersecretory conditions • Initiate at 60 mg once daily and then adjusted to patient's needs [expected max dose of 100 mg once daily]; Take with food
	Aciphex Sprinkle (Rx) • DR capsules: 5 mg, 10 mg	**Treatment of GERD in pediatric patients 1 to 11 years of age for up to 12 weeks** • Dosing for *less than 15 kg*: 5 mg once daily; may increase to 10 mg daily, if inadequate response • For *15 kg or more* the dosing is 10 mg once daily • Take 30 minutes before a meal

Abbreviations: DR, delayed release; DU, duodenal ulcer; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; NSAIDs, non-steroidal anti-inflammatory drugs; ODT, orally disintegrating tablet; OTC, over-the-counter

[a] Listed indications and dosing are per the prescription product labeling; refer to additional dosing guidance for renal and hepatic impairment in Table 4

Methods

Systematic Literature Search

Search strategies were developed by an Informational Scientist for OVID Medline and EMBASE. Strategies consisted of controlled vocabulary, such as MeSH, and keyword phrases. A methodological filter was used for systematic reviews. Results were limited to English language. Databases were searched from 1996 to February 2018. In EMBASE, we excluded conference abstracts. Articles were transferred to EndNote for deduplication. The complete search strategies and terms are available in **Appendix B**.

The lead author also conducted grey literature searching to identify systematic reviews (SRs), such as publications by the Oregon Drug Effectiveness Review Project group and the Agency for Healthcare Research and Quality (AHRQ). We also screened the reference lists and other relevant websites for further information:

I. For grey literature systematic reviews: PubMed Health (https://www.ncbi.nlm.nih.gov/pubmedhealth/)
II. For treatment guidelines addressing PPI therapy: websites of American College of Gastroenterology (ACG), the National Guideline Clearinghouse (https://www.guideline.gov/), and the National Institute for Health and Care Excellence (https://www.nice.org.uk/).
III. For prescribing information product labeling: The Food and Drug Administration website Drugs@FDA: FDA Approved Drug Products (https://www.accessdata.fda.gov/scripts/cder/daf/)
IV. Drug information databases, Micromedex and Lexicomp

Screening

Two reviewers screened publication titles and abstracts. Conflicts were resolved upon discussion between reviewers. The full text for all citations receiving 2 inclusion votes were retrieved. The lead author made the final determination for inclusion upon full-text review. **Figure 1** on page 26 shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

Inclusion and Exclusion Criteria

After identifying a high-quality systematic review (SR) by Oregon Drug Effectiveness Review Project group, published in 2009, additional SRs published from 2009 onward were considered for inclusion. Only SRs providing head-to-head efficacy or safety comparisons (for the approved indications) among the PPIs listed in Table 1 were included. Direct pair-wise meta-analysis data was included, while indirect statistical data was excluded. With regard to *H.pylori* eradication, only SRs including modern treatment regimens, according to the 2017 ACG guideline[10] and where interventions among treatment arms in each trial were fully described (e.g. dose of each drug, duration of regimen) were considered for inclusion. Studies comparing various dosing strategies of the same PPI were excluded. A list containing excluded references is provided in **Appendix C**.

Disease Overview and Treatment Guidelines

Epidemiology— About 15% of adults in the US are estimated to suffer from gastroesophageal reflux disease (GERD), based on self-reported data;[11] whereas, clinically troublesome heartburn is observed in about 6% of the population.[12] In the US, peptic ulcer disease (PUD) is associated with a lifetime prevalence of nearly 12% in men and 10% in women.[13] An estimated 15,000 PUD-related deaths occur each year in the US. The majority of peptic ulcers are attributed to *H.pylori* or NSAID-induced damage. Peptic ulceration occurs in approximately 15–30% of patients on chronic NSAID therapy and can lead to acute complications such as mucosal bleeding.[13]

Treatment with PPIs— Overall, treatment guidelines for the management of GERD, PUD, *H.pylori* eradication, and NSAID-ulcer prevention recommend PPIs as a drug class, without specifying preference for one PPI agent over another.[10,14-16] Guidelines for the use of proton pump inhibitors are outlined in **Table 2.**

Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux disease refers to a family of conditions caused by excessive reflux of gastric acid, pepsin, bile and other digestive enzymes from the stomach.[11] This reflux can lead to erosion and ulceration of the esophagus, chronic esophagitis with bleeding and stricture, Barrett's esophagus, or adenocarcinoma. The American College of Gastroenterology (ACG), defines GERD as "symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung."[12] GERD can be further classified into subtypes, descriptive of the presence of endoscopically-examined erosions: GERD symptoms with non-erosive disease (NERD), or GERD with erosive esophagitis (EE).[12]

Heartburn, regurgitation, and dysphagia are common GERD symptoms, while atypical symptoms include epigastric pain, nausea, bloating, and belching.[12] Extraesophageal manifestations include chronic cough, laryngitis, and dental erosions.[11,12] Patients experiencing daily symptoms tend to have decreased work productivity, loss of sleep, and decreased physical functioning.[12]

The integrity of the esophagogastric sphincter is a main factor that contributes to excessive reflux, whereas gastric acid hypersecretion is "…usually not a dominant factor in the development of esophagitis," with an exception being Zollinger-Ellison Syndrome.[11] Factors such as abdominal obesity, pregnancy, gastric hypersecretory states, delayed gastric emptying, disruption of esophageal peristalsis, and gluttony can exacerbate reflux and symptoms.[11] Aging is directly related to the prevalence and disease severity of erosive esophagitis.[12]

The most recent ACG guideline on the diagnosis and management of GERD expresses that empirical therapy with a PPI can be initiated when a presumptive GERD diagnosis is determined upon observing typical symptoms of heartburn and regurgitation.[12] Endoscopy examination is carried out when the patient presents with alarm symptoms and for patients at

high risk for complications such as those who do not respond to acid suppression.[11,12] The guideline recommends using the Los Angeles (LA) classification system for determining the grade of erosive esophagitis (EE):[12,17]

- Grade A: One or more mucosal breaks ≤ 5 mm, that do not extend between the tops of 2 mucosal folds
- Grade B: One or more mucosal breaks > 5 mm long, but not continuous between the tops of 2 mucosal folds
- Grade C: Continuous mucosal breaks between the tops of 2 or more mucosal folds that involve < 75% of the esophageal circumference
- Grade D: Mucosal breaks which involve ≥ 75% of the esophageal circumference

Pharmacologic therapy—The most effective pharmacotherapies for GERD management are gastric acid secretion inhibitors.[11] Proton pump inhibitors are more potent and efficacious than histamine$_2$ receptor antagonists (H_2RAs).[11] Generally, experts conclude that PPIs are all similarly efficacious in symptom relief and the healing of erosive esophagitis.[11,12,18]

- Gastrologist specialists explain that the frequency and severity of heartburn correlates poorly with the presence or severity of esophagitis.[11] Moreover, " [w]hen GERD treatments are assessed in terms of resolving heartburn, both efficacy and differences among pharmaceuticals are less clear-cut than with the objective of healing esophagitis."[11]

Peptic Ulcer Disease

Peptic ulcer disease (PUD) is often characterized by symptoms of epigastric tenderness, and burning pain exacerbated by fasting.[13] Complications include gastrointestinal bleeding, perforation, and gastric outlet obstruction. PUD may be caused by *H. pylori* infection, NSAID-induced damage, or a multitude of other etiologies (e.g. cytomegalovirus, herpes simplex virus, bisphosphonates, chemotherapy, cocaine, potassium chloride, ischemia, radiation therapy, Crohn's disease, etc.).[13] Ulcers, which may occur in the stomach and/or duodenum, are damaged mucosal areas with active inflammation. More specifically, "[u]lcers are defined as breaks in the mucosal surface >5 mm in size, with depth to the submucosa."[13] The majority of peptic ulcers are attributed to *H. pylori* or NSAID-induced mucosal damage.[13]

Since there are disorders that can mimic PUD, diagnosis confirmation usually employs endoscopic examination. Endoscopy is the most sensitive and specific approach for examining the upper gastrointestinal tract and is performed alongside tissue biopsy to evaluate potential malignancy or *H.pylori* colonization.[13] PPIs can interfere with H. pylori testing, causing a false negative result in a third of cases; thus, they must be discontinued 2 weeks before testing, during which time a histamine-2-receptor blocker can be used.[19]

Pharmacologic therapy— If there is acute bleeding of ulcers, or if other significant endoscopy findings present, intravenous PPI therapy is employed.[19] Once stable, long-term prevention of recurrent bleeding depends on the causative mechanism (*H.pylori*-associated disease, NSAID-associated disease, etc.). When oral PPIs are recommended for temporary or long-term therapy, treatment guidelines do not state a preference for one particular PPI over another.[10,19,20]

H.pylori Infection

H. pylori is associated with chronic gastritis, the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma; although, it is not clear whether eradication decreases gastric cancer rates.[13] Predisposing risk factors for *H.pylori* colonization include low socioeconomic status, increasing number of siblings, having an infected parent, and contaminated water supply.[10] Prevalence is generally lower among non-Hispanic whites compared to African Americans, Hispanic Americans, Native Americans, and Alaska Natives.[10]

There is flexibility for professional judgment in the decision to test for *H. pylori*.[10] Tests to identify active infection include a urea breath test, fecal antigen test, or mucosal biopsy-based testing upon endoscopy. The ACG recommends against screening for *H.pylori* in the setting of GERD.[12]

Pharmacologic therapy—The ACG published guidelines in 2017 on the treatment of *H.pylori* upon performing a systematic review of the evidence.[10] When choosing one of the eight first-line regimen options, the prescriber must take into consideration previous antibiotic exposure. Overall, PPIs are recommended among the triple and quadruple-therapy, first-line options. No preference is specified for any one PPI agent over another.[10] Factors associated with success/failure of eradication of *H.pylori* include the patient's adherence to the multi-drug regimen, side effects, clinical variables (e.g. *CYP2C19* polymorphism, diabetes mellitus, and cigarette smoking). It was found that patients are more likely to comply with the regimen if they are made aware of the benefits, challenges, and potential side effects/adverse events.[10,21] Antibiotic sensitivity of the organism is noted in the ACG guideline as the most important predictor of clinical success.[10]

NSAID-Induced PUD

Injury to the gastroduodenal mucosa occurs from both NSAID prostaglandin modulation and topical insult.[13] Prostaglandins help maintain mucosal integrity.[13] Nearly 5% of patients develop ulcers within 1 year of starting regular use of NSAIDs. Most patients do not experience preceding dyspepsia; thus, there may be an absence of warning signs before ulceration.[13] Risk factors include age > 65 years, history of ulcer, and the concomitant use of glucocorticoids, high-dose NSAIDs, and anticoagulants.[16]

Pharmacologic therapy— Medical intervention for NSAID-related ulcers includes treatment of the active ulcer and prevention of future injury. Stopping NSAID therapy is the first step if possible. When patients must continue chronic NSAID therapy, prevention of ulceration can involve (a) employment of agents that may be less toxic to the gastrointestinal tract (e.g. partially selective NSAIDs associated with a lower risk [e.g. meloxicam], or celecoxib), and (b) the concomitant use of misoprostol or a PPI for patients with low to high gastrointestinal risk.[16] Practitioners must balance cardiovascular and gastrointestinal risks when choosing an NSAID per the patient's comorbidities. The ACG has published guidelines regarding NSAID-induced PUD prevention as described in **Table 2**. Where PPI-concomitant therapy is recommended, there is no preference given to any one particular PPI over another.[16]

Table 2. Guidelines for the Use of Proton Pump Inhibitors

Professional Organization ❖ Guideline	Recommendation for PPI use
American College of Gastroenterology ❖ ACG and CAG Clinical Guideline: Management of Dyspepsia; 2017[22,23]	**Dyspepsia** **Dyspepsia patients <60 year of age:** use empirical PPI therapy if *H. pylori* -negative or for those who are symptomatic after *H. pylori* eradication therapy (HPET) (strong recommendation, high quality evidence) **For functional dyspepsia (FD) patients** who are H. pylori -negative or who remain symptomatic despite HPET, treat with PPI therapy (strong recommendation, moderate quality evidence)
❖ Treatment of Helicobacter pylori Infection; 2017[10]	**Helicobacter pylori (*H.pylori*) Infection** **First-line treatment strategies for providers in North America:** • Triple therapy with a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days is recommended in regions where H. pylori clarithromycin resistance is <15% and in patients with no previous history of macrolide exposure for any reason (Conditional recommendation; low quality of evidence [for duration: moderate quality of evidence]) • Quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10–14 days is a recommended first-line treatment option: This is particularly useful in patients with any previous macrolide exposure or who are allergic to penicillin (strong recommendation; low quality of evidence) • Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10–14 days (strong recommendation; low quality of evidence (for duration: very low quality of evidence)) • Sequential therapy with a PPI and amoxicillin for 5–7 days followed by a PPI, clarithromycin, and a nitroimidazole for 5–7 days (conditional recommendation; low quality of evidence (for duration: very low quality of evidence)). • Hybrid therapy with a PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for 7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (For duration: very low quality of evidence)) • Fluoroquinolone sequential therapy with a PPI and amoxicillin for 5–7 days followed by a PPI, fluoroquinolone, and a nitroimidazole for 5–7 days (conditional recommendation; low quality of evidence (for duration: very low quality of evidence)) • Levofloxacin triple therapy with a PPI, levofloxacin, and amoxicillin for 10–14 days (conditional recommendation; low quality of evidence (For duration: very low quality of evidence)). Eradication should be evaluated using a urea breath test, fecal antigen test or biopsy-based testing at least 4 weeks after the completing treatment and after PPI therapy has been withheld for 1–2 weeks. *Refer to guideline for salvage therapy recommendations*
❖ Diagnosis and Management of Barrett's Esophagus; 2015[14]	**Barrett's Esophagitis (BE)** **PPI Treatment:** Patients with BE should use once-daily PPI therapy; twice-daily dosing is not recommended, other than to improve poor control of reflux symptoms or esophagitis (strong recommendation, moderate level of evidence).

Table 2. Guidelines for the Use of Proton Pump Inhibitors

Professional Organization ❖ Guideline	Recommendation for PPI use
American College of Gastroenterology ❖ Management of Patients with Ulcer Bleeding;2013[19]	**Ulcer Bleeding** **Medical therapy after endoscopy**: Patients with ulcers that have flat pigmented spots or clean bases can receive standard PPI therapy (e.g., oral PPI once daily) (strong recommendation) **Long term prevention of recurrent bleeding ulcers** • In patients with a history of NSAID-associated bleeding ulcers who must resume NSAIDs, a COX-2 selective NSAID at the lowest effective dose plus daily PPI is recommended (Strong recommendation). • In patients with idiopathic (non- H. pylori, non-NSAID) ulcers, long-term antiulcer therapy (e.g., daily PPI) is recommended (conditional recommendation).
❖ Diagnosis and Management of Gastroesophageal Reflux Disease; 2013[12]	**Gastroesophageal Reflux Disease (GERD)** Establishing the diagnosis of GERD • "A presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation. Empiric medical therapy with a proton pump inhibitor (PPI) is recommended in this setting. (strong recommendation, moderate level of evidence)" Management of GERD • Weight loss is recommended for GERD patients who are overweight or have had recent weight gain. (Conditional recommendation, moderate level of evidence) • Head of bed elevation and avoidance of meals 2 – 3 h before bedtime should be recommended for patients with nocturnal GERD. (Conditional recommendation, low level of evidence) • Routine elimination of food that can trigger reflux is not recommended for the treatment of GERD. (Conditional recommendation, low level of evidence) **PPI Therapy** • An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis. <u>There are no major differences in efficacy between the different PPIs. (Strong recommendation, high level of evidence)</u> • Traditional delayed release PPIs should be administered 30 – 60 min before meal for maximal pH control. (Strong recommendation, moderate level of evidence). Newer PPIs may offer dosing flexibility relative to meal timing. (Conditional recommendation, moderate level of evidence) • PPI therapy should be initiated at once a day dosing, before the first meal of the day. (Strong recommendation, moderate level of evidence). <u>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.</u> (Strong recommendation, low level of evidence). o *Non-responders to PPI* should be referred for evaluation. (Conditional recommendation, low level of evidence, see refractory GERD section). o *In patients with partial response to PPI therapy*, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief. (Conditional recommendation, low level evidence). • *Maintenance PPI therapy* should be administered for GERD patients who continue to have symptoms after PPI is discontinued, and in patients with complications including erosive esophagitis and Barrett's esophagus. (Strong recommendation, moderate level of evidence). For patients who require long-term PPI therapy, it

Table 2. Guidelines for the Use of Proton Pump Inhibitors

Professional Organization ❖ Guideline	Recommendation for PPI use
American College of Gastroenterology ❖ *continued*--Diagnosis and Management of Gastroesophageal Reflux Disease; 2013[12]	should be administered in the lowest effective dose, including on demand or intermittent therapy. (Conditional recommendation, low level of evidence) • PPIs are safe in pregnant patients if clinically indicated. (Conditional recommendation, moderate level of evidence) **Potential risks associated with PPIs** • May switch to a different PPIs in the setting of side-effects. (Conditional recommendation, low level of evidence) • Patients with osteoporosis can remain on PPI therapy unless patients have other risk factors for hip fracture. (Conditional recommendation, moderate level of evidence) • PPI therapy can be a risk factor for *C.difficile* so must be used with caution in patients at risk. (Moderate recommendation, moderate level of evidence) • Short-term PPI usage may increase the risk of community-acquired pneumonia; however, there does not yet appear to be elevated risk in long-term users. (Conditional recommendation, moderate level of evidence) • PPI therapy does not need to be altered in concomitant clopidogrel (Strong recommendation, high level of evidence) **H2RA therapy** can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief. Bedtime H2RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but may be associated with the development of tachyphlaxis after several weeks of use. **Surgical options for GERD** can be considered for long-term therapy in GERD patients. Extraesophageal presentations of GERD: Asthma, chronic cough, and laryngitis • GERD can be considered as a potential co-factor in patients with asthma, chronic cough, or laryngitis. Careful evaluation for non-GERD causes should be undertaken in all of these patients. (Strong recommendation, moderate level of evidence). • A PPI trial is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD. (Strong recommendation, low level of evidence)
❖ ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines[24]	**Concomitant Use of PPIs and Thienopyridines** • Risk factors for GI bleeding include advanced age; concurrent use of anticoagulants, steroids, or nonsteroidal anti-inflammatory drugs (NSAIDs); and *H.pylori* infection. A history of prior GI bleeding places patients at highest risk for recurrent bleeding on antiplatelet therapy. Risk of bleeding increases as the number of risk factors increases. • PPIs are recommended to reduce GI bleeding in patients with history of upper GI bleeding or in patients who have multiple risk factors for GI bleeding who require antiplatelet therapy. Routine use of either a PPI or an H2RA is not recommended for patients at lower risk of upper GI bleeding • Decisions regarding concomitant use of PPIs and thienopyridines must balance overall cardiovascular and gastrointestinal risks and benefits • Based on pharmacokinetic and pharmacodynamic studies, using platelet assays as surrogate endpoints, a PPI added to clopidogrel usually reduces the antiplatelet effects with the strongest evidence for an interaction indicating omeprazole/ clopidogrel. However, these surrogate endpoints, have not been established to

Table 2. Guidelines for the Use of Proton Pump Inhibitors

Professional Organization ❖ Guideline	Recommendation for PPI use
American College of Gastroenterology ❖ Prevention of NSAID-Related Ulcer Complications; 2009[16]	cause clinically meaningful differences. Observational studies and a single randomized clinical trial (RCT) have shown inconsistent effects on CV outcomes of concomitant use of thienopyridines and PPIs. Thus, clinically important interaction, particularly in certain subgroups, such as poor metabolizers of clopidogrel, must be taken into consideration. **Prevention of NSAID-Related Ulcer Complications** Recommendations are in regard to the PPI class, and do not specify one particular PPI over another • Patients who absolutely need NSAID therapy at high risk of bleeding (e.g., prior ulcer bleeding or multiple GI risk factors) a COX-2 inhibitor, and co-therapy with misoprostol or high-dose PPI should be considered • Patients with moderate risk can use a COX-2 inhibitor alone or with a traditional nonselective NSAID plus misoprostol or a PPI. • Patients who need NSAID therapy and who also require low-dose aspirin therapy for CVD can use naproxen plus misoprostol or a PPI. • Patients at moderate GI risk who also are at high CV risk should be treated with naproxen plus misoprostol or a PPI.
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition ❖ Pediatric Gastroesophageal Reflux Clinical Practice Guidelines, 2018[25]	• Based on expert opinion, PPIs are recommended as first-line treatment of reflux-related erosive esophagitis in infants and children with GERD (strong recommendation) o Based on expert opinion, a 4–8 week PPI course for treatment of typical symptoms (ie, heartburn, retrosternal or epigastric pain) in children with GERD is recommended • Avoid the use of PPIs for the treatment of (1) crying/distress in otherwise healthy infants, (2) visible regurgitation in otherwise healthy infants, (3) for extraesophageal symptoms (ie, cough, wheezing, asthma), except in the presence of typical GERD symptoms and/or diagnostic testing suggestive of GERD • Use H2RAs in the treatment of reflux related erosive esophagitis in infants and children if PPIs are not available or contraindicated
❖ Joint ESPGHAN/ NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents, 2016[20]	• PPI agents are recommended as a class among several multi-drug regimens listed as first-line options for the treatment of H.pylori infection. Preference for one PPI over another is not specified
National Institute for Health and Care Excellence ❖ Gastro-Oesophageal Reflux Disease: Recognition, Diagnosis and Management in Children and Young People. NICE Guideline, No. 1.; 2015[26]	**Pediatric GERD** **Systematic review** question aimed to assess the comparative effectiveness of proton pump inhibitors compared with placebo and one another in the treatment of GERD for patients <18 years of age? • **No RCT evidence comparing different PPI was found for the pediatric population upon a systematic literature search up to April 2014** General recommendations, based on systematic review of evidence: • Do not offer acid-suppressing drugs (e.g. PPIs, H2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom. • Consider a 4-week trial of a PPI or H2RA for those who are unable to tell you about their symptoms who have overt regurgitation with 1 or more of the

Table 2. Guidelines for the Use of Proton Pump Inhibitors

Professional Organization ❖ Guideline	Recommendation for PPI use
National Institute for Health and Care Excellence ❖ Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Clinical Guideline 184; 2014[18]	following: unexplained feeding difficulties (for example, refusing feeds, gagging or choking) distressed behavior faltering growth. • Consider a 4-week trial of a PPI or H2RA for children and young people with persistent heartburn, retrosternal or epigastric pain. • Assess the response to the 4-week trial of the PPI or H2RA, and consider referral to a specialist for possible endoscopy if the symptoms: do not resolve or recur after stopping the treatment. • **Choosing between PPIs and H2RAs**, take into account: the availability of age-appropriate preparations the preference of the parent (or carer), child or young person (as appropriate) local procurement costs. • Offer PPI or H2RA treatment to infants, children and young people with endoscopy-proven reflux oesophagitis, and consider repeat endoscopic examinations as necessary to guide subsequent treatment. **Adult GERD and PUD** A main review objective, with a systematic search approach, included comparing different PPIs to see which is the most effective in adults to reduce symptoms and reflux exposure **Interventions for GERD** • Offer people a full-dose PPI or 8 weeks to heal severe esophagitis, taking into account the person's preference and clinical circumstances • Offer a full-dose PPI for long-term maintenance treatment for people with severe esophagitis, taking into account the person's preference and clinical circumstances, and the acquisition cost of the PPI. **Interventions for peptic ulcer disease** • Offer *H pylori* eradication therapy to people who have tested positive for *H pylori* and who have peptic ulcer disease. • For people using NSAIDs with diagnosed peptic ulcer, stop the use of NSAIDs where possible. Offer full-dose PPI or H_2RA therapy for 8 weeks and, if *H pylori* is present, subsequently offer eradication therapy.

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; BE, Barrett's esophagus; CAG, Canadian Association of Gastroenterology; CVD, cardiovascular disease; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; GI, gastrointestinal; *H. pylori, Helicobacter pylori*; HPET, *H.pyloi* eradication therapy; H2RA, H2 receptor antagonists; LOE, level of evidence; NICE, National Institute for Health and Care Excellence; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; PUD, peptic ulcer disease; RCT, randomized controlled trial

Pharmacology and Special Populations

Proton pump inhibitors irreversibly inhibit the proton pump (hydrogen potassium ATPase) in gastric parietal cells. This blocks the last step in acid production and ultimately reduces gastric acidity.[3,13] Omeprazole and lansoprazole have been on the market the longest, while newer single-enantiomer products have been designed to improve certain pharmacokinetic features: esomeprazole, the S-enantiomer of omeprazole, and dexlansoprazole, the R-enantiomer of lansoprazole. As shown in **Table 1**, each drug is available in an oral, delayed-release, solid dosage form, while there are also other unique formulations for certain molecules. Powder for suspension formulations are available with esomeprazole magnesium, omeprazole magnesium, and pantoprazole sodium. Lansoprazole is additionally available in an orally disintegrating tablet. Delayed-release capsule formulations can usually be opened and the contents mixed into certain soft foods or liquids, however, the product labeling should be referred to for the specific allowances and administration instructions for each product.

Delayed-release dexlansoprazole has a dual-release system, resulting in two plasma-concentration peaks at about 2 and 5 hours after administration.[2] The other agents generally have peak concentrations between 1 and 6 hours. These products have a prolonged pharmacodynamic action reflecting sustained, irreversible inhibition of the proton pump as the duration of effect is expected to last 72 to 96 hours.[8,13] According to product labeling, most PPIs must be administered before or with a meal, except for rabeprazole DR tablets when used for GERD indications,[8] dexlansoprazole,[2] and pantoprazole DR tablets[7] which may be taken without regard to food.[2,7,8] However, the ACG GERD guideline recommends that all single-ingredient PPIs, excluding dexlansoprazole, should be administered 30 to 60 minutes before a meal, when used for the treatment of GERD.[12]

Pharmacokinetic parameters for the PPI agents are included in **Table 3**. Each PPI is metabolized by cytochrome P450 (CYP) 2C19 and 3A4. Renal elimination clears mostly inactive PPI metabolites, thus, renal dose adjustments are not required for mild to moderate renal impairment. Further information regarding use in special populations is summarized in **Table 4**.

Table 3. Pharmacokinetic Parameters of Oral Proton Pump Inhibitors

Generic Name Brand Name	Bioavailability Tmax Protein binding Volume of Distribution	Half-life[a] (hrs)	Metabolism	Excretion
Dexlansoprazole[2] Dexilant DR capsule	BA: NR Tmax: 2 peaks; 1 to 2 hr & 4 to 5 hr PB: 96-99% V_D: 40 L	1-2	Extensively metabolized in the liver, via reduction and **CYP2C19-** and **CYP 3A4-**mediated oxidation; An *in vivo* study mainly in CYP2C19 extensive and intermediate metabolizers showed that DEX did not affect the pharmacokinetics of diazepam a CYP2C19 substrate	Urine: 50.7% of dose, all as metabolites Feces: 47.6%
Esomeprazole magnesium[3] Nexium DR capsule Nexium DR granules for oral suspension	BA: 90% with repeated dosing PB: 97% Tmax: 1.6 hr V_D: 16 L	1-1.5	Extensively metabolized in the liver via **CYP2C19** and **CYP 3A4**; Co-administration of ESO 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in diazepam clearance.	Urine: 80% of dose as inactive metabolites; 1% as parent drug Feces: ~20% of dose as inactive metabolites
NOTE: PK parameters for both formulations do not differ				
Esomeprazole strontium[4] Generic DR capsule	BA: NR PB: 97% Tmax: 1.7 hr V_D: 16 L	1-1.5	Extensive metabolism via **CYP2C19** and **CYP 3A4**; expected to interfere with CYP2C19 metabolized drugs	Urine: 80% of dose as inactive metabolites; 1% as parent drug Feces: ~20% of dose as inactive metabolites
Lansoprazole[5] Prevacid DR capsules Prevacid Solutab DR ODT	BA: >80% PB: 97% Tmax: 1.7 hr V_D: NR	1.5 ±1.0	Metabolized via **CYP2C19** and **CYP 3A4** to inactive or minimally active metabolites; a PK study showed a decrease in the AUC of clopidogrel (CYP2C19 substrate) with LAN concomitant administration	Urine: 30% of dose as metabolites with negligible activity Feces: 66% of dose
NOTE: PK parameters for both formulations do not differ				

Table 3. Pharmacokinetic Parameters of Oral Proton Pump Inhibitors

Generic Name Brand Name	Bioavailability Tmax Protein binding Volume of Distribution	Half-life[a] (hrs)	Metabolism	Excretion
Omeprazole[6] Prilosec DR capsule Prilosec DR tablet Prilosec granules for oral suspension	BA: 30-40% (first-pass metabolism); increases with repeat administration PB: 95% Tmax: DR capsules, 0.5 to 3.5 hrs V_D: NR NOTE: all products are enteric-coated granules with similar PK	0.5-1	**CYP2C19** is the major pathway, followed by **CYP3A4** to inactive or minimally active metabolites; OME is a time-dependent inhibitor of CYP2C19	Urine: 77% of dose primarily as metabolites Feces: 33%
Pantoprazole sodium[7] Protonix DR tablet Protonix granules for oral suspension	BA: 77% PB: 98% Tmax: • DR tablet: 2.5 hr • DR suspension: 2 - 2.5 hr V_D: 11-23.6 L NOTE: DR tablets and suspension with similar PK	1	**CYP2C19** is the major pathway, followed by **CYP3A4** to inactive metabolites	Urine: 71% of dose all as inactive metabolites Feces: 18%
Rabeprazole sodium[8,9] Aciphex DR Tablet Aciphex DR Sprinkle Capsule	BA: • Aciphex DR tablet: 52% • Aciphex Sprinkle: Not available PB: • Aciphex DR tablet: 96.3% • Aciphex Sprinkle: Not available Tmax: • Aciphex DR tablet: 2-5 hrs • Aciphex Sprinkle: 2.5 hr (1-6.5 hr) V_D: NR	1-2	A significant portion undergoes non-enzymatic reduction to a thioether compound; other pathways included **CYP3A** & **CYP2C19** to thioether and sulphone metabolites with negligible activity	Urine: 90% of the dose as metabolites Feces: 9.8% of the dose as metabolites

Abbreviations: BA, Bioavailability; DEX, dexlansoprazole; DR, delayed release; ESO, esomeprazole; LAN, lansoprazole; IR, immediate release; NR, not reported in the package insert; ODT, orally disintegrating tablets; OME, omeprazole; OTC, over the counter product; PB, protein binding; PK, pharmacokinetic parameters; Tmax, time to peak plasma concentration; V_D, volume of distribution

[a] All agents have sustained activity

Table 4. Special Populations Considerations for PPIs per Product Labeling[2-9]

Generic Name	Pediatric age and Indication	Geriatric	Hepatic and Renal Impairment	Pregnancy and Nursing
Dexlansoprazole	Indicated for pediatric patients ≥12 years of age for the following: healing of EE, maintenance of healed EE, and relief of heartburn associated with symptomatic non-erosive GERD	No differences noted in clinical trials although a greater sensitivity in some older individuals cannot be ruled out	Renal: No adjustment Hepatic: Child-Pugh A: No adjustment Child-Pugh B: A dose reduction to 30 mg daily is recommended for healing of EE Child-Pugh C: dexlansoprazole is not recommended	Pregnancy: Fetal risk cannot be ruled out Breast Feeding: Infant risk cannot be ruled out
Esomeprazole strontium	Safety and effectiveness has not been established in children. Strontium competes with intestinal absorption of calcium and incorporation into bone. Safety studies in children have not been performed; use in children is not recommended	No differences noted in clinical trials although a greater sensitivity in some older individuals cannot be ruled out	Renal: For mild to moderate renal impairment, no adjustment is needed. Studies evaluating the PK and safety of strontium in patients with severe renal impairment is lacking, so use is not recommended. Hepatic: No information	Pregnancy Category C Distribution to breast milk: Yes; Infant risk cannot be ruled out Consider risk vs. benefit
Esomeprazole magnesium	Established for short-term treatment of EE due to acid-mediated GERD in children age ≥1 month Established for short-term treatment of heartburn and other symptoms associated with GERD in children age ≥ 1 year	No differences noted in effectiveness or adverse events in clinical trials although a greater sensitivity in some older individuals cannot be rules out	Renal: no adjustments recommended Hepatic: Child-Pugh A,B: No adjustment Child-Pugh C: no more than 20 mg once daily	Pregnancy: Fetal Risk cannot be ruled out Breast Feeding: Infant Risk cannot be ruled out
Lansoprazole	Established for the healing of EE and the treatment of symptomatic GERD (e.g. heartburn) for pediatric patients age ≥ 1 year	No differences noted in effectiveness or adverse events although a greater sensitivity in some older individuals cannot be rules out	Renal: No adjustment required Hepatic: Child-Pugh C: recommended dose is 15 mg once daily	Pregnancy Category B: Fetal Risk cannot be ruled out Breast Feeding: Infant Risk cannot be ruled out

Table 4. Special Populations Considerations for PPIs per Product Labeling[2-9]

Generic Name	Pediatric age and Indication	Geriatric	Hepatic and Renal Impairment	Pregnancy and Nursing
Omeprazole	Established for treatment of EE in pediatric patients ≥ 1 month of age Established for maintenance of healing of EE and for symptomatic GERD (e.g. heartburn) for pediatric patients ≥ 1 year of age	No differences noted in effectiveness or adverse events in clinical trials although a greater sensitivity in some older individuals cannot be rules out	Renal: No clinically meaningful problems expected with CrCl 10-62 mL/min Hepatic (Child-Pugh Class A, B or C): for maintenance of healing of EE use omeprazole 10 mg once daily	Pregnancy: Fetal Risk cannot be ruled out Breast Feeding: Infant Risk cannot be ruled out
Pantoprazole sodium	Established for pediatric patients ≥ 5 years old for the short-term treatment in the healing and symptomatic relief of EE associated with GERD	Moderate increase in AUC (43%) and Cmax (26%) No dosing adjustment required	Renal-based dose adjustments are not necessary Hepatic-based dose adjustments are not necessary for doses up to 40 mg/day. Higher doses have not been studied with this condition	Pregnancy Category C Breast Feeding: Infant risk cannot be ruled out
Rabeprazole sodium	Aciphex Sprinkle: indicated for children age 1 to 11 years for treatment of GERD Aciphex Tablet: indicated for adolescents ≥ 12 years old for short-term treatment of symptomatic GERD	No differences noted in effectiveness or adverse events in clinical trials although a greater sensitivity in some older individuals cannot be ruled out	No dosing adjustment is recommended in mild to moderate hepatic impairment. There is not adequate information in patients with severe impairment (Child-Pugh Class C) Dose adjustments for renal impairment are not necessary of up to 20 mg/daily dosage	Pregnancy: Fetal risk cannot be ruled out Breast Feeding: Infant risk cannot be ruled out

Abbreviations: DR, delayed release; EE, erosive esophagitis; GERD, gastroesophageal reflux disease;

Efficacy

I. Evidence Summary Points

This subsection condenses the comparative evidence findings. The next section, *'II. Systematic Review Evidence for the Efficacy of PPIs,'* and Table 1 of Appendix E describe the included SRs in greater detail.

GERD-Related Outcomes

With respect to the treatment of GERD in pediatric patients, the 2015 NICE guideline incorporated a systematic review to compare the efficacy of different PPIs.[26] Authors did not report any RCTs available comparing PPIs head-to-head in the pediatric population experiencing GERD.

The following information summarizes evidence for the adult population based on 8 additional SRs identified.

Dexlasoprazole Comparisons

- A pair-wise meta-analysis for only one direct comparison (dexlansoprazole 60 mg/day vs. lansoprazole 30 mg/day) is available and shows no significant difference between treatments for the 8 week complete healing rate of erosive esophagitis (EE).[27] A 2017 SR shows no additional RCTs, comparing dexlansoprazole with any other PPI, unaccounted for in the previously mentioned SR meta-analysis.[28]

Esomeprazole (ESO) Comparisons

Lansoprazole (LAN) versus ESO

- Two random-effects meta-analyses showed no significant difference for the 8 week complete healing rate of EE when comparing ESO 40 mg/day vs. LAN 30 mg/day, regardless of disease severity.[27,29] However, one of these meta-analyses reported a significant difference for the week 4 complete healing rate, in favor of esomeprazole, regardless of disease severity.[29]
- There was consistent SR evidence (Mei et al, 2016, and McDonagh et al, 2009) reporting a significant difference in favor of ESO 20 mg/day vs. LAN 15 mg/day for the outcome of EE relapse rates at 6 months.[29-32]
- An SR (McDonagh et al) reported no significant difference in the pooled effect estimate for ESO 40 versus LAN 30 for the outcome of complete symptom relief at week 4.[29]

Omeprazole (OME) versus ESO

- Four SR meta-analyses are all consistent with one another, showing a pooled effect estimate favoring ESO 40 mg/day versus OME 20 mg/day with respect to the proportion of patients with healed EE at week 4 and 8.[29,33-36] However, there were inconsistent findings when the lower 20 mg/daily dose of esomeprazole was considered.[29,34,36]
- Two SR meta-analyses regarding symptom resolution at week 4 in patients with erosive GERD reported pooled effect estimates in favor ESO 40 mg/day versus OME

20 mg/day, and no difference found between ESO 20 mg/day and OME 20 mg/day.[29,36]

- Two systematic reviews found no differences between ESO 20 or 40 mg/day versus OME 20 mg/day for the resolution of heartburn symptoms at week 4 in patients with non-erosive GERD.[29,34]

Pantoprazole (PAN) versus ESO

- No significant difference was found between ESO 40 mg/day versus PAN 40 mg/day for the proportion of patients with EE healed at week 8, based on a single meta-analysis and on results from newer-published RCTs identified by a 2017 SR.[28,29]
- No differences were found regarding GERD symptoms in patients with EE or non-erosive esophagitis, based on 1 SR.[29]

Rabeprazole (RAB) versus ESO

- No efficacy differences between ESO vs. RAB have been reported.

Additional Lansoprazole Comparisons

- No significant difference in EE-healing efficacy at 8 weeks, EE relapse rates, or resolution of GERD symptom resolution at week 4 between LAN 30 mg/day and OME 20 mg/day was found.[29]
- McDongah et al SR found no significant differences between LAN 30 mg/day and PAN 40 mg/day for EE healing at week 4 and 8, or for GERD resolution at week 4.[29]

Additional Omeprazole Comparisons

- No significant differences were found between OME 20 mg/day versus PAN 20 mg/day or PAN 40 mg/day with respect to EE healing at week 4 or 8, or for the resolution of GERD symptoms at week 4.[29]
- There is consistent SR evidence showing no difference in the week 8 healing rate for OME versus RAB. In addition, McDonagh et al found 1 RCT showing no significant difference in relapse rates at week 52 between OME 20 mg/day versus RAB 10 or 20 mg/day.[29,37]
- One SR suggests there is a significant difference in favor of RAB 20 mg/day compared to OME 20 mg/day for GERD-related symptom resolution.[38]

Peptic-Ulcer- Related Outcomes

Based on 3 SRs included, there were no differences between PPIs for the 4-week healing rate of duodenal ulcers.[29,39,40] No head-to-head, comparative SR evidence was found for PPIs in the specific setting for the healing of NSAID-induced ulcers.[29]

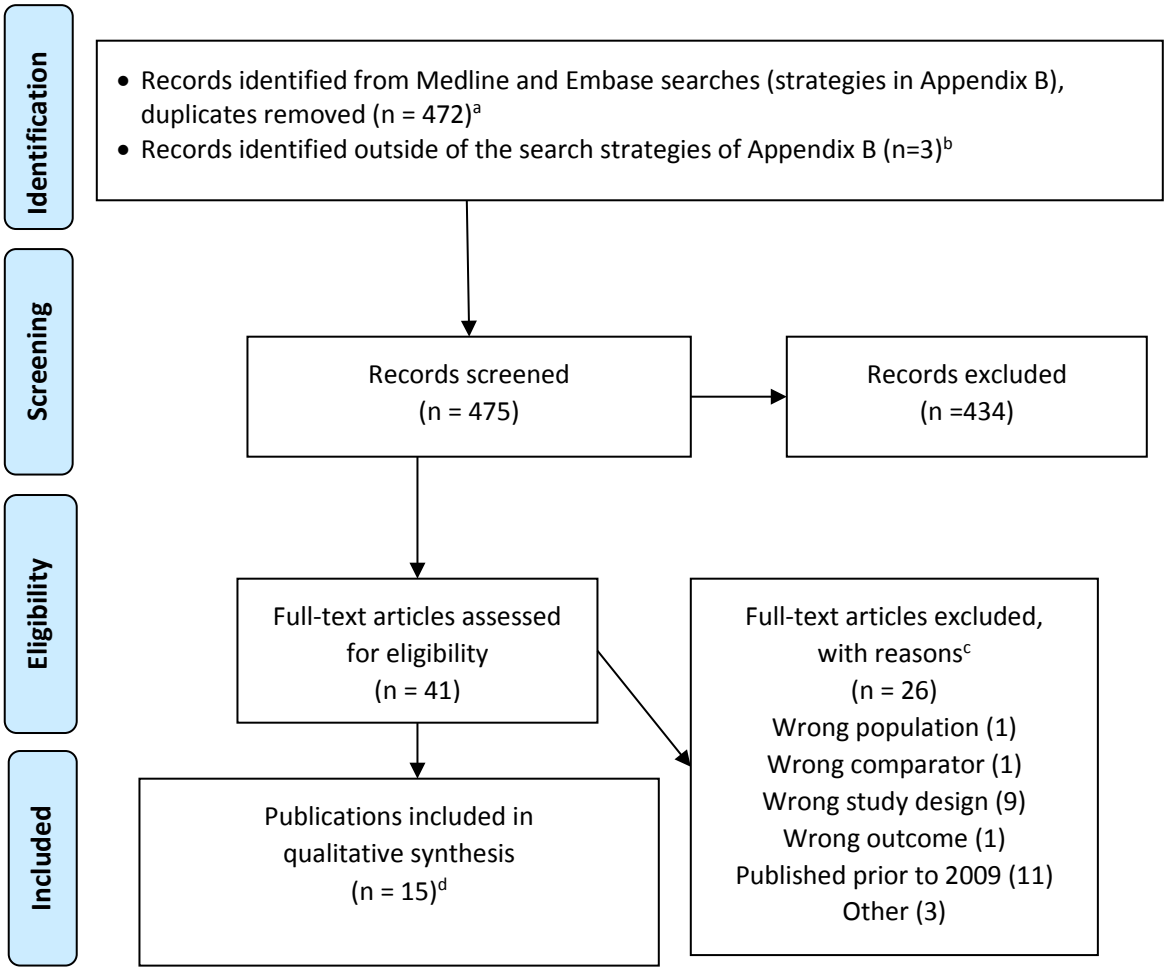
Prevention of NSAID-induced Ulcer

Two SRs found no significant differences reported between any PPI vs. PPI comparison.[29,41]

II. Systematic Review Evidence for the Efficacy of PPIs

Our literature search yielded a total of 475 unique titles. After identifying the high-quality 2009 SR (McDonagh et al), published by the Center for Evidence Based Policy at Oregon Health and Science University, 14 additional SRs that were more recently published were selected for inclusion. **Figure 1** displays the PRIMSA flow chart for the publication screening process. **Appendix C** provides a list of studies excluded in the full-text review stage.

Figure 1. PRISMA Flow Chart for Publication Screening



[a] Combined results from Medline and Embase search strategies after duplicates removed in Endnote®

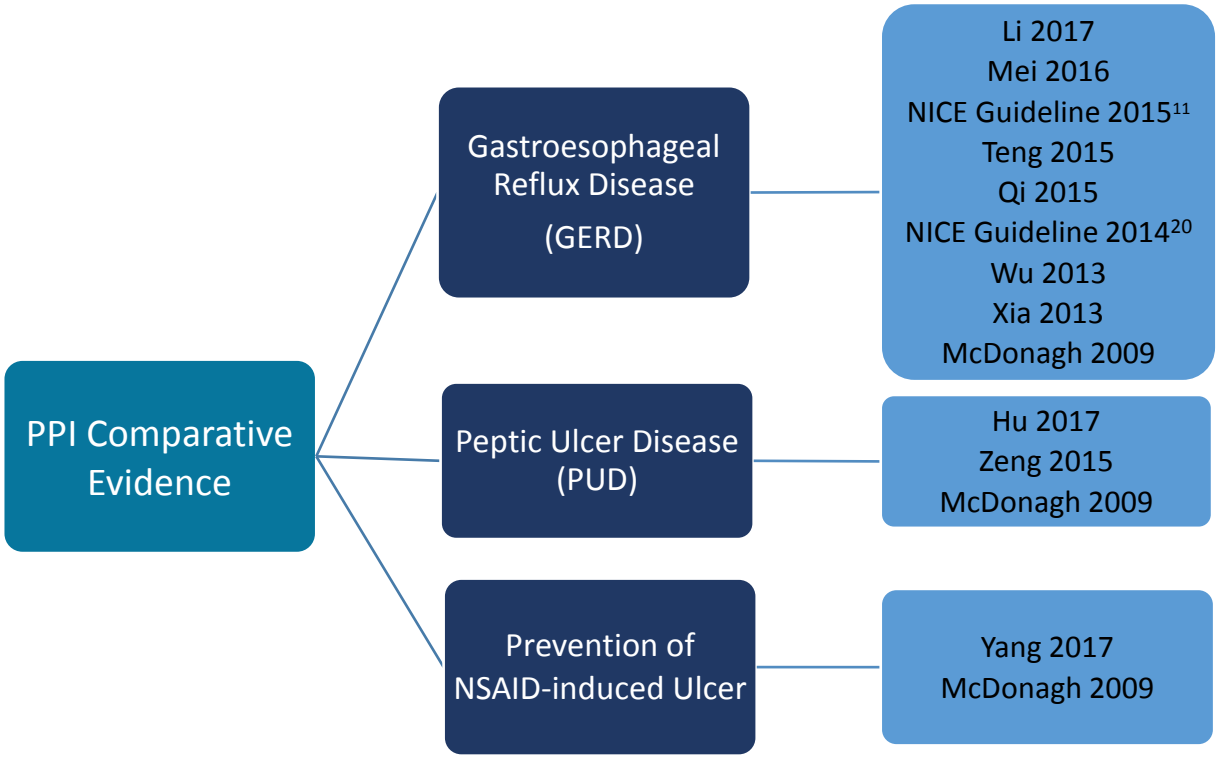
[b] One publication was a systematic drug class review by McDonagh et al, Drug Effectiveness Review Project, Oregon Health & Science University; and two publications were systematic reviews conducted for the National Institute for Health and Care Excellence (NICE) clinical guideline for adult GERD[18] and pediatric GERD[26]

[c] See Appendix C for descriptions

[d] (n=15); 12 unique SRs are included in the *Efficacy* section of the report, while the remaining 3 SRs[42-44] are included in the *Safety* discussion of the report

Figure 2. Publications Included to Describe the Comparative Efficacy Between PPIs

	Indication Area	Systematic review first author and publication year



Efficacy evidence is provided according to the following treatment areas:

A. Healing and Symptom Relief of Erosive Esophagitis and Non-erosive Esophagitis Associated with GERD
B. Treatment of Peptic Ulcers
C. Prevention of NSAID-induced ulcer
D. *H.pylori* eradication

Within each of these main indication areas, there is further breakdown to reflect applicable head-to-head comparisons and the various outcomes reported. PPI comparisons are ordered alphabetically. Drugs are abbreviated by the first three letters of their generic name. Numerical values follow to indicate the daily dose compared (e.g. DEX 60 versus LAN 30 means dexlansoprazole 60 mg/day versus lansoprazole 30 mg/day).

A. Healing and Symptom Relief of Erosive Esophagitis and Non-erosive Esophagitis Associated with GERD

With respect to the treatment of GERD in pediatric patients, the 2015 NICE guideline incorporated a systematic review with the objective of comparing the efficacy between different PPIs.[26] The authors did not report any RCTs available comparing PPIs in the pediatric subpopulation experiencing GERD.

The following information is a summary of the PPI head-to-head evidence for the adult population, based on the remaining 8 SRs identified addressing GERD-related treatment outcomes.

DEXLANSOPRAZOLE

Dexlansoprazole (DEX) versus Lansoprazole (LANS)

i. Healing of erosive esophagitis (endoscopy confirmed)

A direct meta-analysis by Wu et al, 2013, found no significant difference in the 8 week complete healing rate of erosive esophagitis between treatments with DEX 60 vs. LAN 30 for all LA grades A-D or for high-grades C and D.[27]

Dexlansoprazole (DEX) versus Other PPIs: Systematic review searches by Wu et al, 2013, and Li et al, 2017, are consistent with one another in that no other direct evidence is available regarding dexlasoprazole vs. other PPIs in the setting of erosive esophagitis, aside from the comparison with lansoprazole previously discussed.[27,28] Note that dexlasoprazole is only approved for the management of GERD and not for other disorders such as peptic ulcer disease or *H.pylori* eradication.

ESOMEPRAZOLE

Esomeprazole (ESO) versus Lansoprazole (LAN)

i. Healing of erosive esophagitis (endoscopy confirmed)

A direct meta-analysis by Wu et al, 2013, found no significant difference in the 8 week complete healing rate of erosive esophagitis between treatment with ESO 40 vs. LAN 30 when analyzing patients of all LA grades A-D together and when analyzing patients with high-grade disease C and D.[27] The meta-analysis by McDonagh et al, 2009, is consistent with the finding for the 8 week healing rate (based on their random-effects outcome) regardless of disease severity at baseline. However, when assessing moderate to high grade disease severity, McDonagh et al, and the 2014 NICE guideline authors[45] found a significant difference in favor of esomeprazole at week 8, as a result of different RCTs included in the meta-analyses. In addition, McDonagh et al evaluated differences at week 4 and report a significant difference in favor of esomeprazole, regardless of baseline disease severity.[46-48]

- Systematic review searches by both Wu et al 2013 and Li et al 2017 are consistent with one another in that the same 4 publications were found regarding ESO vs. LAN in the setting of erosive esophagitis and no additional publications were identified.[27,28]

ii. Maintenance therapy to prevent relapse of esophagitis in patients with endoscopically proven erosive GERD (endoscopy confirmed)

Two systematic reviews (Mei et al, 2016, and McDonagh et al, 2009) reported consistent findings. A significant difference was found in favor of ESO 20 vs. LAN 15 for the outcome of EE relapse rates at 6 months based on 2 RCTs.[29-32]

iii. GERD symptom resolution and time to sustained relief in patients with erosive GERD

The SR by McDonagh et al, 2009, reported no significant difference in the pooled effect estimate for ESO 40 versus LAN 30 for the outcome of complete symptom relief at week 4.[29] No more recent RCTs were found by Li et al, 2017, that could supplement this pooled outcome.[28] Moreoever, McDonagh et al, note that results from 3 individual RCTs did not favor one product over the other for the outcome of "time to sustained relief of heartburn symptoms associated with erosive esophagitis," defined as the first of 7 consecutive days without heartburn.[29]

Esomeprazole (ESO) versus Omeprazole (OME)

i. Healing of erosive esophagitis

Four SR meta-analyses are all consistent with one another, showing a pooled effect estimate favoring ESO 40 versus OME 20 with respect to the proportion of patients healed at week 4 and 8.[29,33-36] There were inconsistent findings when the lower dose of esomeprazole was used. Teng et al 2015 found a significant difference in favor of ESO 20 versus OME 20 at week 8, however, Qi et al, 2015, and McDonagh et al, 2009, found no significant difference.[29,34] This discrepancy perhaps resulted from authors entering in different event rates into their meta-analysis calculation with respect to a particular RCT (Kahrilas et al 2000).

No additional RCTs were found by a 2017 SR (Li et al) for this comparison/outcome that were not already accounted for in these 4 SRs with earlier publication dates.[28]

- *Healing in the moderate to severe EE subpopulation*— McDonagh et al, 2009 and the 2014 NICE SR[18,45] found no significant differences between ESO 20 vs. OME 20. However, meta-analysis by McDonagh et al showed a significant difference in the pooled effect estimate for healing in moderate to severe EE at week 4 and 8 favoring ESO 40 (versus OME 20).[29]

ii. GERD symptom resolution and time to sustained relief in patients with erosive GERD

Two SR meta-analyses that were found regarding erosive GERD symptom resolution at week 4 are consistent in that the pooled effect estimates favor ESO 40 versus OME 20, and no differences were found between ESO 20 and OME 20.[29,36] McDonagh et al, also report 3 studies each individually finding that a greater proportion of ESO 40 treated patients achieved sustained relief by day 14 or 28 compared to the OME 20 group.[29]

- McDonagh et al, 2009, pooled effect estimate was in favor of ESO 40 versus OME 20 on the outcome of complete symptom relief at 4 weeks [pooled risk difference was 8% (95%

CI 3 to 13), and a number needed to treat of 13]. However, no difference was found between ESO 20 and OME 20.[29] Qi et al, 2015, is consistent with these findings.[36]

*iii. Heartburn symptom resolution in patients with **non-erosive** (endoscopy negative) GERD*

Two systematic reviews found no differences between ESO 20 or 40 versus OME 20 for the resolution of heartburn symptoms at week 4 week in patients with non-erosive GERD based on 1 RCT.[29,34]

Esomeprazole (ESO) versus Pantoprazole (PAN)

i. Healing of erosive esophagitis

The meta-analysis by McDonagh et al, 2009, resulted in a significant difference in favor of ESO 40 versus PAN 40 for the proportion of patients healed at week 4, however, there was no difference at week 8. Two more recent RCTs not included in the McDonagh et al SR were identified by Li et al, 2017, SR.[28] Both of these RCTs also reported no significant difference in the rate of endoscopic healed esophagitis between ESO 40 and PAN 40 treatment groups at week 8.[49,50]

- *Healing in the moderate to severe EE subpopulation*— McDonagh et al, 2009, report mixed evidence on the pooled-effect differences between ESO 40 vs. PAN 40. At 4 weeks, the ESO 40 arm had a significantly higher healing rate than PAN 40 arm; however, at week 8, no difference was found.[29]

*ii. Maintenance therapy to prevent **relapse** of esophagitis in patients with endoscopically proven erosive GERD*

There are mixed findings regarding the maintenance of symptomatic and endoscopic remission at 6 months for ESO 20 versus PAN 20 in adults, however, the dose of pantoprazole at 20 mg per day is lower than the approved adult dosing for this indication.[29,30,33] No SR evidence was found that compared ESO 20 to PAN 40 for this outcome.

iii. GERD symptom resolution at 4 weeks in patients with erosive GERD

McDonagh et al, 2009, reported no significant difference in the pooled effect estimate for ESO 40 versus PAN 40 for complete erosive GERD symptom relief at week 4.

*iv. Heartburn symptom resolution in patients with **non-erosive** (endoscopy negative) GERD*

McDonagh et al, 2009, reported results from an RCT showing that PAN 20 was non-inferior to ESO 20 for the time to first and sustained GERD symptom relief.[51]

Esomeprazole (ESO) versus Rabeprazole (RAB)

Based on SRs by Li et al, 2017, and Qi et al, 2016, it appears that esomeprazole has not been compared to rabeprazole in a head-to-head RCT for the management of erosive esophagitis. Only 1 SR (McDonagh 2009) reports information about this comparison, however, it is with regard to non-erosive GERD. No difference was found in the time to first-24 hour period without symptoms of heartburn or regurgitation for ESO 20 versus RAB 10 in patients with non-erosive esophagitis.[29,52]

LANSOPRAZOLE

Lansoprazole (LAN) versus Omeprazole (OME)

i. Healing of erosive esophagitis

McDonagh, et al, 2009, reported no significant difference between LAN 30 vs. OME 20, or OME 40 for the pooled-effect estimate for the proportion of patients healed at week 4 and 8. The SR by Li, et al 2017, found one additional RCT published after McDonagh et al, which also showed no significant difference in healing between LAN 30 and OME 20 at week 8.[28,49]

- *Healing in the moderate to severe EE subpopulation*— McDonagh et al SR meta-analysis found no significant differences between LAN 30 vs. OME 20

ii. Maintenance therapy to prevention relapse of esophagitis in patients with endoscopically proven erosive GERD

McDonagh et al reported 1 RCT showing no significant difference in relapse rates between LAN 30 versus OME 20 mg with treatment lasting 48 weeks.[29,53]

iii. GERD symptom resolution at 4 weeks in patients with erosive GERD

McDonagh et al found no significant difference between LAN 30 versus OME 20 or 40 with respect to symptom resolution at 4 weeks, based on 1 RCT.[29]

Lansoprazole (LAN) versus Pantoprazole (PAN)

i. Healing of esophagitis

McDonagh et al found no significant difference between LAN 30 versus PAN 40 for the percent of patients healed at week 4 and 8 based on 1 RCT.[29]

ii. GERD symptom resolution at 4 weeks in patients with erosive GERD

McDonagh et al found 2 RCTs total, which both individual reported no significant difference between LAN 30 versus PAN 40 with respect to symptom resolution at week 4.[29]

Lansoprazole (LAN) versus Rabeprazole (RAB)

It appears that lansoprazole and rabeprazole have not yet been compared head-to-head in a randomized controlled trial.[28]

OMEPRAZOLE

Omeprazole (OME) versus Pantoprazole (PAN)

i. Healing of erosive esophagitis

With respect to the percent of patients healed at week 4 and 8, McDonagh et al found 2 studies showing no significant difference between OME 20 versus PAN 20 or PAN 40, respectively.[29] An additional RCT not identified by McDonagh et al that was found by the Li et al SR also showed no significant differences between OME 20 vs. PAN 40 for the 4 and 8 week healing rate.[28,54]

ii. GERD symptom resolution at 4 weeks in patients with erosive GERD

With respect to symptom resolution at 4 weeks McDonagh et al found 1 study showing no significant difference between OME 20 versus PAN 20 and 2 studies showing no significant difference between OME 20 and PAN 40.[29] An additional RCT not identified by McDonagh et al, which was found by the Li et al SR also showed no significant differences between OME 20 vs. PAN 40 for improvement in the principal symptoms of reflux at week 2 and 4.[28,54]

Omeprazole (OME) versus Rabeprazole (RAB)

i. Healing of erosive esophagitis

Three studies were identified by McDonagh et al comparing OME 20 vs RAB 10 or 20. Meta-analysis pooled-effect estimates showed no significant difference between OME 20 vs. RAB 10 or 20 for the percent of patients healed at week 4 and 8.[29] Xia et al, 2013 SR, also showed no significant difference in endoscopic relief of erosive GERD at week 8 for the comparison of OME 20 vs. RAB 20.[38] No more recent studies were identified from Li et al, 2017 SR.[28]

ii. Maintenance therapy to prevent relapse of esophagitis in patients with endoscopically proven erosive GERD

McDonagh et al found 1 RCT comparing relapse rates at week 52 between OME 20 versus RAB 10 or 20 treatment arms and found no significant diffence.[29,37]

iii. GERD symptom resolution in patients with erosive GERD

The SR by McDonagh et al showed no significant difference between OME 20 and RAB 20 with respect to GERD symptom resolution at 4 weeks based on 1 study. However, a newer SR including additional studies found a significant difference in the pooled-effect estimate for the outcome of GERD-related heartburn relief in favor of RAB 20. A limitation of this finding was the significant statistical heterogeneity.[38]

B. Treatment of Peptic Ulcers

Duodenal Ulcers

An SR meta-analysis by Hu et al, 2017, found no significant differences in the week 4 duodenal ulcer healing rate for direct comparisons between OME 20 versus LAN 30, PAN 40, or RAB 20.[39] There was no head-to-head comparison data for other PPI comparisons. The SR by McDonagh et al, 2009, is consistent with Hu et al, finding no significant differences in the pooled effect for the week 4 duodenal ulcer healing rate between OME 20 and LAN 30. In addition, 1 RCT for the following comparisons was identified by McDonagh et al, each showing no difference in duodenal ulcer healing at week 4: OME 20 vs. PAN 40, OME 20 vs. RAB 20, and OME 40 vs. ESO 40.

One SR (Zeng et al, 2015) comparing LAN and OME for the treatment of *H.pylori*-associated duodenal ulcer found no significant difference in duodenal ulcer healing rate between treatment arms.[40]

Gastric Ulcers

McDonagh et al note their inclusion of 3 fair-quality trials comparing omeprazole to rabeprazole. Each trial found no significant difference in healing rates at 6 or 8 weeks. No other studies of at least fair quality were identified for other PPI comparisons.[29]

NSAID-related Ulcers

The SR by McDonagh et al found no head-to-head comparison studies for PPIs in this setting for healing of NSAID-induced ulcers.[29]

- The PPIs with specific FDA-approval for the treatment of active peptic ulcers include lansoprazole, omeprazole, and rabeprazole.

C. Prevention of NSAID-induced Ulcer

Esomeprazole and lansoprazole are the PPIs with an FDA-approval for risk reduction of NSAID-associated gastric ulcers. Nonetheless, the 2009 ACG guideline on the prevention of NSAID-related ulcer complications recommends PPIs, as a class, for patients at moderate to high risk of bleeding. Overall, the guideline does not specify preference of any one PPI over another. Among the systematic reviews identified for this indication, no significant differences were identified between any two PPIs.[29,41]

- The SR by Yang et al, 2017, included studies directly comparing PPIs in patients taking NSAIDs, with the primary outcome of endoscopic peptic ulceration.[41] Three direct comparison studies were identified: 2 comparing ESO 20 vs. OME 20 and another comparing OME 20 vs. PAN 20 or 40.[55,41] The pair-wise meta-analysis for these comparisons showed no significant efficacy differences with respect to the risk of endoscopic peptic ulceration. No other studies were identified that directly compared other PPIs.[41] The SR by McDonagh et al is consistent with the findings by Yang et al, as authors found no significant differences for OME vs. PAN[55] based on the same trial.[29]

D. *H.pylori* Eradication

There were a few SRs that were considered for inclusion which compared some PPIs for the eradication of *H.pylori*.[34,40,56] Studies included out-of-date treatment regimens with respect to the current ACG 2017 guideline for the treatment of *H.pylori* or didn't fully delineate regimen duration or dosing of each drug; thus, these SRs were ultimately excluded. Most relevant to today's current first-line options, the ACG guideline states that there is insufficient evidence comparing modern treatment regimens.[10] As discussed in the background section, the ACG guideline gives no preference for any one PPI agent over another when incorporated into *H.pylori* eradication regimens.[10] Dexlansoprazole and pantoprazole are the only PPIs without an FDA-indication for the eradication of *H.pylori*.

III. Genetic Factors

Polymorphisms of CYP2C19, a main enzyme involved with PPI metabolism, affect the activity of this enzyme and can theoretically impact outcomes related to PPI therapy. It is estimated that 3% of Caucasians and 15 to 20% of Asians demonstrate a CYP2C19 poor metabolizer phenotype.[3] The poor metabolizer phenotype may result in increased PPI exposure, and thus more extensive acid inhibition. However, authors of the 2017 ACG *H.pylori* treatment guideline comment that the change in effect magnitude due to CYP2C19 polymorphisms in North America has not been fully elucidated.[10] GERD clinical outcomes related to CYP2C19 polymorphism is a topic of a recent literature review. A 2016 SR meta-analysis showed that the CYP2C19 rapid metabolizer phenotype was associated with an increased risk of experiencing erosive esophagitis refractory to PPI therapy compared with poor metabolizers. Authors propose individualizing PPI therapy based on CYP2C19 genotype.[57]

Safety

Long-term use of PPIs has been associated with a higher incidence of *Clostridium difficile*, and the development of hip fractures in older women.[13] Other potential adverse effects include mild to moderate hypergastrinemia,[58] vitamin B12 deficiency,[59] magnesium deficiency, and decreased calcium and iron absorption.[11,13] There is also debate whether dementia is associated with long-term use of PPIs; however, more robust studies are needed.[44]

The ACG 2013 GERD guideline provides the following recommendations regarding the use of PPIs and adverse effects; however, some of these clinical outcomes such as the cardiovascular effects of a PPI in combination with clopidogrel are still debated.[12,42]

- Consider switching to a different PPI upon experience of side effects to the initial chosen PPI.
- Patients with osteoporosis can continue PPI therapy; concern for hip fracture should be exercised mainly for patients with additional risk factors for hip fracture. (Strong recommendation, moderate level of evidence)
- PPIs should be used with caution in patients with *C.difficile* infection risk. (Strong recommendation, moderate level of evidence)
- Although short-term PPI usage may increase the risk of community acquired pneumonia, risk does not appear elevated in long-term users. (Conditional recommendation, moderate level of evidence)
- PPI therapy does not need to be altered when used concomitantly with clopidogrel since clinical data does not support an increased risk for adverse cardiovascular events. (Strong recommendation, high level of evidence)

Table 5 summarizes the warnings and precautions provided in the labeling for PPIs in addition to the FDA-warnings issued pertaining to PPI safety.

Table 5. Warnings and Precaution Labeling for PPIs[3,5-9]

Warnings in Common for All PPI Products[a]	▪ ***Clostridium difficile*-Associated Diarrhea**: PPI therapy may increase risk[60] ▪ **Cyanocobalamin (Vitamin B-12) Deficiency**: daily long-term use (e.g. longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin ▪ **Hypomagnesemia**: there are rare case reports with prolonged PPI treatment[61] ▪ **Bone Fracture**: long-term and multiple daily dose PPI therapy may increase the risk of osteoporosis-related fractures of the hip, wrist, or spine ▪ **Gastric Malignancy**: Consider additional follow-up and diagnostic testing since symptomatic response to PPI therapy does not rule out malignancy ▪ **Acute Interstitial Nephritis**: observed in some patients taking PPIs ▪ **Cutaneous and Systemic Lupus Erythematosus (CSLE)**: CSLE has been reported in patients taking PPIs—most being cutaneous type. Patients generally improve with discontinuation of the PPI ▪ **Interaction with Methotrexate**: PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity ▪ **Concomitant Use with Warfarin**: Monitor for increases in INR and prothrombin time ▪ Interaction with diagnostic investigation for neuroendocrine tumors: pause PPI therapy at least 14 days before assessing chromogranin A levels

Table 5. Warnings and Precaution Labeling for PPIs[3,5-9]

FDA Safety Communications	▪ 2012: FDA Drug Safety Communication: Clostridium difficile diarrhea can be associated with PPI use[60] ▪ 2011: FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of PPIs[61] ▪ 2011: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. According the March 2011 update, the FDA decided not to place a warning on OTC PPIs since the risk with short-term, low dose use was determined to be unlikely.[62]

[a]Refer to prescribing information for full details and recommended monitoring with respect to warnings/precautions; drug interaction warnings for each PPI are provided in Appendix D.

Adverse-Event Outcomes

Five of the included SRs with efficacy outcomes also had direct comparisons with respect to PPI safety; most of these are regarding esomeprazole comparisons. For the treatment of GERD, adverse events related to esomeprazole are comparable to those involved with lansoprazole, pantoprazole and omeprazole based on 3 SRs:[30,34,36]

- Mei et al, 2016, designed a systematic review to compare esomeprazole 20 mg/day to other PPIs for the maintenance of GERD with treatment lasting at least 6 months. Authors found 2 RCTs reporting drug-related adverse event (DRAE) rates: one comparing ESO 20 vs. LAN 15, and another comparing ESO 20 vs. PAN 20. No significant differences in DRAE rates were found for either comparison.[30]
- The SR by Teng et al, 2015, compared esomeprazole versus omeprazole for the healing of EE, including trials of shorter duration (outcomes taken at 4 and 8 weeks) compared to Mei et al. Authors state that upon pooling data on adverse events from all the included studies accounting for a total of 9200 patients, the safety profiles of esomeprazole and omeprazole were similar. There were no significant differences in the pooled estimates of treatment-associated adverse effects for ESO versus OME with respect to abdominal pain, diarrhea, flatulence, or headache.[34]
- Qi et al, 2015, SR compared ESO vs. OME tolerability, defined as discontinuation, for any reason, from a study drug during therapy for erosive esophagitis. The fixed-effects meta-analysis showed no significant difference between treatment groups overall or by any subgroup according to dose of each agent.[36]

One SR, by Xia et al, comparing RAB 20 and OME 20 for the maintenance GERD therapy lasting up to 8 weeks concluded no significant difference in adverse events upon meta-analysis.[38]

The 2009 SR by McDonagh et al is consistent with the findings above as the authors conclude no significant differences found between any particular PPI comparison based on short-term or long-term studies available.[29]

Drug-Drug Interactions (DDI)

Professional prescribing information for each PPI, warns about potential drug interactions with antiretrovirals, digoxin, drugs dependent on gastric pH for absorption, methotrexate, tacrolimus, warfarin, and strong CYP2C19 or CYP3A4 inducers and inhibitors. **Appendix D** provides the specific labeling advice (e.g. use caution, contraindicated, or dose adjustment required) for each PPI with regard to specific drug molecules.

DDI with Clopidogrel

In general, there is response variability to clopidogrel on a population level due to genetic variation in CYP2C19. There may also be response variability when other drugs that are metabolized by CYP2C19 are administered concomitantly with clopidogrel, however, there seems to be "mixed and inconclusive evidence regarding a small increase in mortality and readmission rate for coronary events in patients receiving a PPI while on clopidogrel."[12,13,63]

Two SRs were identified concerning the impact of concomitant PPI use with particular CYP-metabolized drugs. Based on subgroup meta-analysis, Niu et al, 2017, concluded that the risk of major cardiovascular events (MACEs) was significantly increased when clopidogrel was combined with omeprazole, lansoprazole, esomeprazole, pantoprazole, however, not with rabeprazole, during the management of coronary artery disease.[42] Authors also performed subgroup analysis with respect to CYP2C19 genotype and found that rapid metabolizers were at an increased risk of MACEs when exposed to PPI and clopidogrel concomitant therapy.[42] Yucel et al (SR published in 2016) advise clinicians that the interaction risk with clopidogrel can be reduced by considering PPIs with lesser affinity for CYP2C19 metabolism (e.g. pantoprazole or rabeprazole as preferred compared to omeprazole).[43]

Other DDIs

With respect to potential interactions with other drugs (e.g. protease inhibitors, and mycophenolate) Yucel et al conclude that there is inconclusive evidence among systematic reviews from a prospective clinical-outcomes standpoint, despite some observational or pharmacokinetic data suggesting otherwise.[43] They express the need for well conducted randomized controlled trials in various settings with relevant clinical outcomes (e.g. HIV-related mortality and viral suppression, transplant rejection, etc.) and stratification to compare individual PPI molecules, as well as longitudinal studies to integrate the factor of time.[43]

Summary

All PPIs are FDA-approved for the erosive esophagitis healing, prevention of EE relapse and for the symptomatic relief associated with GERD. Table 1 and Table 4 summarize the indicated age groups with respect to each formulation. Some PPIs have FDA-approval for healing of certain peptic ulcers (lansoprazole, omeprazole, and rabeprazole). Two PPIs have FDA approval for the prevention of NSAID-associated ulcers (esomeprazole and lansoprazole) and all PPIs except dexlansoprazole and pantoprazole are approved for *H.pylori* eradication to reduce the risk of duodenal ulcer recurrence. Despite fewer approved indications for some agents compared to others, PPIs are recommended among treatment guidelines for the management of GERD, healing of PUD, prevention NSAID-related ulcers, and the eradication of *H.pylori* without preference of one agent over another.

Upon reviewing systematic literature, there were some efficacy differences found between certain doses of different PPIs for GERD related outcomes; these are summarized beginning on page 24. Regarding PUD efficacy outcomes, there were no differences between PPIs for the 4-week healing rate of duodenal ulcers,[29,39,40] nor where there any studies identified reporting significant differences for the healing of gastric ulcers or the prevention of NSAID-induced ulcers.

Authors of the 2013 ACG GERD guideline concluded that PPIs are similarly efficacious for the recommended 8 week course of therapy for symptom relief and healing of erosive esophagitis. This conclusion is provided based on a high level of evidence grade, "implying that further research was unlikely to change the authors' confidence in the estimate of the effect."[12] The 2017 ACG guideline gives no preference for any one PPI agent over another when incorporated into *H.pylori* eradication regimens,[10] as there is a paucity of evidence comparing PPIs individually among modern treatment regimens. Moreover, guidelines do not prefer one agent over another for the prevention of NSAID-induced ulcers.

The long-term use of PPIs has been associated with a higher incidence of community and hospital acquired *Clostridium difficile*, and the development of hip fractures in older women.[13,64] Other potential side effects include mild to moderate hypergastrinemia,[58] vitamin B12 deficiency,[59] magnesium deficiency, and decreased calcium and iron absorption.[11,13]

Five of the SRs included direct comparisons with respect to the PPI tolerability; most of these are regarding esomeprazole comparisons. For the treatment of GERD, the adverse events related to esomeprazole are comparable to those involved with lansoprazole, pantoprazole and omeprazole treatment, based on 3 SRs:[30,34,36] One SR, comparing rabeprazole and omeprazole for the maintenance GERD therapy lasting up to 8 weeks concluded no significant difference in adverse events upon meta-analysis.[38] The 2009 SR by McDonagh et al is consistent with the findings above as the authors conclude no significant differences found between any particular PPI comparison based on short-term and long-term studies available.[29]

Professional prescribing information for each PPI, warns about potential drug interactions with antiretrovirals, digoxin, drugs dependent on gastric pH for absorption, methotrexate, tacrolimus, warfarin, and strong CYP2C19 or CYP3A4 inducers and inhibitors. **Appendix D** provides the specific labeling advice for each PPI with regard to specific drug molecules.

Appendix A

Table 1. Indication Comparison Chart for Proton Pump Inhibitors

	GERD (hEE, MhEE, sGERD)	Gastric Ulcer	Duodenal Ulcer	Hypersecretory conditions (e.g. Zollinger Ellison syndrome	*H.pylori* eradication to reduce risk of DU recurrence	NSAID associated gastric ulcer	Heartburn symptoms
Dexlansoprazole[2]	X						X (Rx)
Esomeprazole magnesium[3]	X			X	X	X (pNU)	X (Rx and OTC)
Esomeprazole strontium[4]	X			X	X	X (pNU)	X (Rx)
Lansoprazole[5]	X	X (hGU, hNU)	X (hDU, MhDU, hNU)	X	X	X (pNU, hNU)	X (Rx and OTC)
Omeprazole[6]	X	X (hGU)	X (hDU)	X	X		X (Rx and OTC)
Pantoprazole	X			X			X (Rx)
Rabeprazole[8]	X		X (hDU)	X	X		X (Rx)

Abbreviations: DU, duodenal ulcer; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; hDU, healing of duodenal ulcers; hEE, healing of erosive esophagitis; hGU, healing of gastric ulcer; hNU, healing of NSAID-related gastric ulcers; MhDU, maintenance of healed duodenal ulcer; MhEE, maintenance of healed erosive esophagitis; OTC, over the counter formulation; pNU, prevention of NSAID-related ulcers; Rx, prescription formulation; sGERD, symptomatic relief of GERD

[a] Note that the indication may be product specific for the specified drug moiety; See Table 1 in the full-text of the report for indications per formulation

Appendix B: Literature Search Strategies

Table 1. Ovid Medline Literature Search Strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) Searched performed in February		
1	*proton pump inhibitors/	5572
2	proton pump inhibitor?.ti,kw,kf.	4061
3	or/1-2 [CLASS-Precise]	6832
4	proton pump inhibitors/	9128
5	proton pump inhibitor?.ti,ab,kw,kf.	11585
6	or/4-5 [CLASS-Sensitive]	14926
7	*dexlansoprazole/ or *esomeprazole/ or *lansoprazole/ or *omeprazole/ or *rabeprazole/	4307
8	(dexlansoprazol$ or esomeprazol$ or lansoprazol$ or omeprazol$ or pantoprazol$ or rabeprazol$).ti,kw,kf.	4302
9	or/7-8 [DRUGS-Precise]	5756
10	dexlansoprazole/ or esomeprazole/ or lansoprazole/ or omeprazole/ or rabeprazole/	7839
11	(dexlansoprazol$ or esomeprazol$ or lansoprazol$ or omeprazol$ or rabeprazol$).ti,ab,kw,kf.	8630
12	or/10-11 [DRUGS-Sensitive]	10714
13	exp Gastroesophageal Reflux/	17445
14	exp Esophagitis/	5916
15	exp peptic ulcer/ or duodenal ulcer/ or stomach ulcer/	18319
16	(esophagitid$ or esophagiti$).ti,ab,kw,kf.	8165
17	(GERD or ((gastroesophageal or Gastro-oesophageal or gastro-esophageal) adj2 (reflux or disease?))).ti,ab,kw,kf.	18795
18	((peptic? or gastro* or gastric$ or stomach* or duoden*) adj2 ulcer?).ti,ab,kw,kf.	20260
19	or/13-18 [INDICATIONS]	55294
20	Helicobacter infections/	24860
21	Helicobacter pylori/	28270
22	((helicobacter$ adj2 (pylori? or infection?)) or (Hpylori? or H-Pylori?) or campylobacter pylori).ti,ab,kw,kf.	35410
23	*Helicobacter infections/ or *Helicobacter pylori/ [foccused]	25970
24	or/20-22 [H-PYLOR- Sensitive]	38315
25	or/22-23 [H-Pylori - Precise]	36667

26	Meta-Analysis/	80863
27	(metaanaly$ or meta-analy$).ti,ab,kw,kf.	119339
28	((systematic adj3 review) or (overview adj4 review)).ti,kw,kf.	81371
29	(cochrane$ or systematic review?).jw.	14966
30	(or/26-29) and English.la. [SR FILTER]	180245
31	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	889432
32	exp animals/ not humans.sh.	2170987
33	(animal? or beaver? or beef or bovine or breeding or bull or canine or castoris or cat or cattle or cats or chicken? or chimp$ or cow or dog or dogs or equine or feline? or foal or foals or fish or insect? horse or horses or livestock or mice or monkey? or mouse or murine or plant or plants or pork or porcine or protozoa? or purebred or rat or rats or rodent? or sheep or simian? or thoroughbred).ti. or veterinar$.ti,ab,kw,kf,hw.	1143910
34	(31 not (or/32-33)) and English.la. [Cochrane RCT Filter 6.4.d SP-Max & additional Animal exclusions]	751497
35	(2008$ or 2009$ or 2010$ or 2011$ or 2012$).yr. [Pub Year 2008-2012]	4157015
36	(2013$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$).yr. [Pub Year 2013-2018]	5530324
37	12 and 30 [Drugs-Sensitive & SR]	165
38	12 and (or/19,24) and 30 [Drugs-sensitive & Indications-H-Pylori & SR]	128
39	**9 and 30 [Drugs-Precise & SR]**	**55**
40	9 and (or/19,24) and 30 [Drugs Precise & Indications-H-Pylori & SR]	50
41	6 and (or/19,24) and 30 [Class-Sensitive & Indications-HPylori & SR Filter]	421
42	**3 and (or/19,24) and 30 [Class-Precise & Indications-H-pylori & SR Filter]**	**251**

Table 2. EMBASE Search Strategy

Searches performed in February 2018		
Line #	Search Terms	Results
1	proton pump inhibitor'/mj OR 'proton pump inhibitor*':ti,ab,kw 22072	22,072
2	dexlansoprazole'/de OR 'esomeprazole'/mj OR 'lansoprazole'/mj OR 'omeprazole'/mj OR 'pantoprazole'/mj OR 'rabeprazole'/mj 13548	13,548
3	dexlansoprazol*':ti,ab,kw OR 'esomeprazol*':ti,ab,kw OR 'lansoprazol*':ti,ab,kw OR 'omeprazole*':ti,ab,kw OR 'pantoprazol*':ti,ab,kw OR 'rabeprazol*':ti,ab,kw 18270	18,270
4	gastroesophageal reflux'/exp/mj OR 'esophagitis'/exp/mj OR 'peptic ulcer'/exp/mj OR 'duodenum ulcer'/mj OR 'stomach ulcer'/mj 107838	107,838
5	esophagitid*:ti,ab,kw OR esophagiti*:ti,ab,kw 19367	19,367
6	gerd:ti,ab,kw 14532	14,532
7	((gastroesophageal OR 'gastro-oesophageal' OR 'gastro-esophageal') NEAR/2 (reflux OR disease*)):ti,ab,kw 32232	32,232
8	((stomach* OR gastro* OR duoden* OR stomach*) NEAR/2 ulcer*):ti,ab,kw 33760	33,760
9	#4 OR #5 OR #6 OR #7 OR #8 140412	140,412
10	helicobacter pylori'/mj 25193	25,193
11	helicobacter infection'/mj 16040	16,040
12	((helicobacter* NEAR/2 (pylori* OR infection* OR gastrit* OR nemestrina*)):ti,ab,kw) OR hpylori*:ti,ab,kw OR 'h pylori*':ti,ab,kw OR 'campylobacter pylori*':ti,ab,kw 55306	55,306
13	#10 OR #11 OR #12 56689	56,689
14	1996:py OR 1997:py OR 1998:py OR 1999:py OR 2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py 20647346	206,473,346
15	(cochrane*:jt OR 'systematic review*':jt OR 'meta analysis'/mj OR 'systematic review'/mj OR ((systematic NEAR/3 review):ti) OR 'meta analys*':ti,ab,kw OR metaanalys*:ti,ab,kw OR ((overview NEAR/4 (review OR reviews)):ti)) NOT ('conference abstract'/it OR 'conference review'/it) AND [english]/lim 175497	175,497
16	('clinical study'/mj OR 'clinical trial'/mj OR 'controlled clinical trial'/mj OR 'controlled study'/mj OR 'major clinical study'/mj OR 'randomized controlled trial'/mj OR 'control group'/mj OR (((clinical OR randomi* OR controlled OR multicentre OR multicenter OR 'multi centre' OR 'multi center') NEAR/3 (study OR trial)):ti,ab) OR placebo:ab,ti OR 'head to head':ti,ab) AND [english]/lim 860544	860,544
17	animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de NOT ('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de AND ('human'/exp OR 'human cell'/de)) 6399086	6,399,086
18	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de 2600470	2,600,470
19	conference abstract'/it OR 'conference review'/it 2885611	2,885,611

20	#16 NOT (#17 OR #18 OR #19) 608384	608,384
21	#1 AND (#9 OR #13) AND #14 AND #15 324	324
22	#21 AND (2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) 114	114
23	(#2 OR #3) AND #14 AND #15 172	172
24	#23 AND (2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) 52	52
25	#22 OR #24 144	144
26	(#2 OR #3) AND #20 AND (2013$:py OR 2014$:py OR 2015$:py OR 2016$:py OR 2017$:py OR 2018$:py) 579	579
27	#1 AND (#9 OR #13) AND #20 AND (2013$:py OR 2014$:py OR 2015$:py OR 2016$:py OR 2017$:py OR 2018$:py) 273	273
28	#26 OR #27 597	597

Appendix C: Excluded Studies

Wrong Population

1. Barletta JF, Bruno JJ, Buckley MS, Cook DJ. Stress Ulcer Prophylaxis. *Critical care medicine.* 2016;44(7):1395-1405.

Wrong Comparator

2. Neumann I, Letelier LM, Rada G, et al. Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. *The Cochrane database of systematic reviews.* 2013(6):Cd007999.
    - Doesn't address oral PPI vs oral PPI use. Study questions are different as they focus on low vs high dose and route, oral vs IV

Wrong Outcome

3. Kirchheiner J, Glatt S, Fuhr U, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. *Eur J Clin Pharmacol.* 2009;65(1):19-31.

Wrong Study Design

4. Alkim H, Iscan M, Oz F. Effectiveness of ranitidine bismuth citrate and proton pump inhibitor based triple therapies of Helicobacter pylori in Turkey. *Libyan j.* 2011.
5. Bardou M, Fortinsky KJ. Safety of medication options for treating pediatric esophagitis. *Expert opinion on drug safety.* 2015;14(7):1087-1096.
    - No head-to-head PPI evidence
6. Edwards SJ, Lind T, Lundell L, Das R. Systematic review: standard- and double-dose proton pump inhibitors for the healing of severe erosive oesophagitis -- a mixed treatment comparison of randomized controlled trials. *Alimentary pharmacology & therapeutics.* 2009;30(6):547-556.
7. Jiang YX, Chen Y, Kong X, Tong YL, Xu SC. Maintenance treatment of mild gastroesophageal reflux disease with proton pump inhibitors taken on-demand: a meta-analysis. *Hepato-gastroenterology.* 2013;60(125):1077-1082.
    - Dose frequency effect study
8. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of Proton Pump Inhibitor Drugs for Inducing Clinical and Histologic Remission in Patients With Symptomatic Esophageal Eosinophilia: A Systematic Review and Meta-Analysis. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2016;14(1):13-22.e11.
    - No direct head to head study evidence; does subgroup analysis (indirect comparison); trial not designed to capture direct head-to-head evidence per Prospero protocol
9. McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. *Alimentary pharmacology & therapeutics.* 2012;36(5):414-425
10. Nagaraja V, Eslick GD. Evidence-based assessment of proton-pump inhibitors in Helicobacter pylori eradication: a systematic review. *World journal of gastroenterology.* 2014;20(40):14527-14536.
11. Sun S, Cui Z, Zhou M, et al. Proton pump inhibitor monotherapy and the risk of cardiovascular events in patients with gastro-esophageal reflux disease: a meta-analysis. Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society. 2017;29(2).
    - Indirect PPI vs PPI comparison evidence by subgroup analysis; studies included were PPI vs. non-PPI arm
12. Yaghoobi M, Padol S, Yuan Y, Hunt RH. Impact of oesophagitis classification in evaluating healing of erosive oesophagitis after therapy with proton pump inhibitors: a pooled analysis. *Eur J Gastroenterol Hepatol.* 2010;22(5):583-590.

Published prior to 2009

13. Edwards SJ, Lind T, Lundell L. Systematic review of proton pump inhibitors for the acute treatment of reflux oesophagitis. *Alimentary pharmacology & therapeutics.* 2001;15(11):1729-1736.
14. Edwards SJ, Lind T, Lundell L. Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Alimentary pharmacology & therapeutics.* 2006;24(5):743-750.
15. Edwards SJ, Lind T, Lundell L, et al. Systematic review of proton pump inhibitors for the maintenance of healed reflux oesophagitis. *Journal of Outcomes Research.* 2002;6(1 14):1-14.
16. Gralnek IM, Dulai GS, Fennerty MB, Spiegel BM. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2006;4(12):1452-1458.
17. Klok RM, Postma MJ, van Hout BA, Brouwers JR. Meta-analysis: comparing the efficacy of proton pump inhibitors in short-term use. *Alimentary pharmacology & therapeutics.* 2003;17(10):1237-1245.
18. Lauritsen K, Deviere J, Bigard MA, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. *Alimentary pharmacology & therapeutics.* 2003;17(3):333-341.
19. Salas M, Ward A, Caro J. Are proton pump inhibitors the first choice for acute treatment of gastric ulcers? A meta analysis of randomized clinical trials. *BMC Gastroenterol.* 2002;2:17.
20. Sharma VK, Leontiadis GI, Howden CW. Meta-analysis of randomized controlled trials comparing standard clinical doses of omeprazole and lansoprazole in erosive oesophagitis. *Alimentary pharmacology & therapeutics.* 2001;15(2):227-231.
21. Vakil N, Fennerty MB. Direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease. *Alimentary pharmacology & therapeutics.* 2003;18(6):559-568.
22. Wang WH, Huang JQ, Zheng GF, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. *World journal of gastroenterology.* 2005;11(26):4067-4077.
23. Wang WH, Huang JQ, Zheng GF, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. *World journal of gastroenterology.* 2005;11(26):4067-4077.

Other

24. Chuang TW, Chen SC, Chen KT. Current status of gastroesophageal reflux disease: Diagnosis and treatment. *Acta Gastro-Enterologica Belgica.* 2017;80(3):396-404.
    - Library unable to provide interlibrary loan
25. Petryszyn P, Staniak A, Grzegrzolka J. Is the use of esomeprazole in gastroesophageal reflux disease a cost-effective option in Poland? *Journal of comparative effectiveness research.* 2016;5(2):169-178.
    - The search strategy of the article was limited, there is some selective reporting, while other SRs seem more robust and capture more completely the available evidence
26. Wojcik P, Chudziak D, Macioch T, Niewada M. Systematic Review of Esomeprazole for The Treatment of Gastroesophageal Reflux Disease. *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2015;18(7):A622.
    - Research abstract only; full text not available

Appendix D: PPI Drug Interaction Warnings

Table 1. Labeled Drug Interactions Warnings for PPIs

<table>
<tr><th>Generic Name</th><th>Drug Interaction</th></tr>
<tr><td>Dexlansoprazole[2]</td><td>
Antiretrovirals:
• Rilpivirine, Atazanavir, Nelfinavir exposure may be decreased, reducing antiviral effect and promoting the development of drug resistance
o Rilpivirine – concomitant use is contraindicated
o Atazanavir – see atazanavir labeling for dose adjustment instructions
o Nelfinavir – avoid concomitant use
• Saquinavir exposure may be increased with potential for toxicity
o See prescribing information monitor for potential toxicities
• Other retrovirals: See prescribing information

Digoxin: Potential increased digoxin exposure. Consider TDM

Drugs dependent on gastric pH for absorption (e.g iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetel, ketoconazole/itraconazole): Absorption may be reduced. Use caution with mycophenolate mofetil in transplant patients as active metabolite exposure may be reduced (clinical relevance unknown)

Methotrexate: May increase exposure of methotrexate and/or its metabolite with potential toxicities. Consider withdrawal of dexlansoprazole

Tacrolimus: Potential for increased exposure, especially in transplant patients with intermediate/poor CYP2C19 metabolism. Consider TDM

Warfarin: Increased INR & PT; potential for abnormal bleeding and death

<u>ENZYME INTERACTIONS</u>
Use of strong CYP2C19 or CYP3A4 inducers (e.g. St. John’s Wort, rifampin, ritonavir-containing products) may result in decreased dexlansoprazole exposure
Use of strong CYP2C19 or CYP3A4 inhibitors (e.g. voriconazole) may result in increased exposure of dexlansoprazole

<u>LABORATORY INTERACTIONS</u>
In testing for neuroendocrine tumors, false positive chromogranin A (CgA) levels may result. Stop dexlansoprazole 14 days prior and repeat test if positive result.
In secretin stimulation tests, gastrin hypersecretion may result suggesting false positive for gastrinoma. Stop dexlansoprazole 30 days prior to testing.

In urine testing for THC, a false positive screening test may occur. Use alternative confirmatorymethods to verify results.
</td></tr>
<tr><td>Esomeprazole magnesium[3]</td><td>
Antiretrovirals
• Concomitant use with atazanavir and nelfinavir is not recommended
o Atazanavir plasma concentration may substantially reduced, resulting in a loss of therapeutic effect and development of drug resistance
• Concomitant use with saquinavir may result in increased drug concentrations; monitoring for toxicity and consider dose reduction
<table>
<tr><td>Nelfinavir</td><td>AUC ↓ 36%</td><td>Cmax ↓37%</td><td>Cmin ↓39%</td></tr>
<tr><td>Atazanavir</td><td>AUC ↓ 94%</td><td>Cmax ↓ 96%</td><td>Cmin ↓ 95%</td></tr>
<tr><td>Saquinavir/ritonavir</td><td>AUC↑ 82%</td><td>Cmax ↑ 75%</td><td>Cmin ↑ 106%</td></tr>
</table>
o Rilpivirine – concomitant use is contraindicated
o Atazanavir – see prescribing information
o Nelfinavir – avoid concomitant use
• Saquinavir exposure may be increased with potential for toxicity
o See prescribing information monitor for potential toxicities
</td></tr>
</table>

Table 1. Labeled Drug Interactions Warnings for PPIs

Generic Name	Drug Interaction
	Cilostazol: May increase systemic exposure of cilostazol and active metabolite. Consider cilostazol dose reduction Clopidogrel: Reduced exposure of clopidigrel active metabolite via CYP2C19 inhibition. Avoid the combination Concomitant therapy with Clarithromycin/Amoxicillin: See clarithromycin prescribing information Diazepam: Inhibition of CYP2C19 may result in a 45% decrease in diazepam clearance (CYP2C19 substrate) Digoxin: Bioavailability of digoxin may increase.Consider TDM Drugs dependent on gastric pH for absorption (e.g iron salts, erlotinib, mycophenolate mofetel, ketoconazole): Absorption may be decreased. Methotrexate: Serum levels of methotrexate and its metabolite may be increased and prolonged, increasing the risk of methotrexate toxicity. Consider withdrawal of esomeprazole, especially with high-dose methotrexate therapy. Mycophenolate mofetil: A reduction in exposure to the active metability (mycophenolic acid) may occur. Clinical implications for organ rejection are not established. Tacrolimus: Serum levels of tacrolimus may increase Warfarin: A clinically significant interaction has not been shown, however, post-marketing reports of INR/PT changes suggest monitoring may be appropriate **LABORATORY INTERACTIONS** In testing for neuroendocrine tumors, false positive chromogranin A (CgA) levels may result. Stop esomeprazole before assessing CgA levels. Repeat CgA leves if they are high. **ENZYME INTERACTIONS** Use of strong CYP2C19 or CYP3A4 inducers may result in decreased esomeprazole exposure. Avoid concomitant use with St. John's Wort or rifampin Use of strong CYP2C19 or CYP3A4 inhibitors (e.g. voriconazole) may result in increased exposure of Esomeprazole.
Lansoprazole[5]	Antiretrovirals: • Rilpivirine, Atazanavir, Nelfinavir o Rilpivirine – concomitant use is contraindicated o Atazanavir – see prescribing information o Nelfinavir – avoid concomitant use • Saquinavir exposure may be increased with potential for toxicity o See prescribing information monitor for potential toxicities • Other retrovirals: See prescribing information Combination therapy with Clarithromycin & Amoxicillin: Combination of lansoprazole and clarithromycin can lead to serious adverse reactions, including potentially fatal arrhythmias. Use is contraindicated. Evaluate amoxicillin drug interactions Digoxin: Potential increased digoxin exposure. Consider TDM Drugs dependent on gastric pH for absorption (e.g iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetel, ketoconazole/itraconazole): Absorption may be reduced. Use caution with mycophenolate mofetil in transplant patients as active metabolite exposure may be reduced (clinical relevance unknown) Methotrexate: May increase exposure of methotrexate (especially at high dose) and/or its metabolite with potential toxicities. Consider withdrawal of lansoprazle Sucralfate: A delay in absorption of lansoprazle may occur. Take lansoprazle at least 30 minutes prior to sucralfate Tacrolimus: Potential for increased exposure, especially in transplant patients with intermediate/poor CYP2C19 metabolism. Consider TDM Theophylline: Increased clearance of theophylline. Consider TDM

Table 1. Labeled Drug Interactions Warnings for PPIs

<table>
<tr><th>Generic Name</th><th>Drug Interaction</th></tr>
<tr><td></td><td>Warfarin: Increased INR & PT; potential for abnormal bleeding and death; Monitor PT/INR
<u>LABORATORY INTERACTIONS</u>
In testing for neuroendocrine tumors, false positive chromogranin A (CgA) levels may result. Stop lansoprazle 14 days prior and repeat test if positive result.
In secretin stimulation tests, gastrin hypersecretion may result suggesting false positive for gastrinoma. Stop lansoprazle 28 days prior to testing.
In urine testing for THC, a false positive screening test may occur. Use alternative confirmatory methods to verify results.

<u>ENZYME INTERACTIONS</u>
Use of strong CYP2C19 or CYP3A4 inducers may result in decreased lansoprazle exposure. Avoid concomitant use of lansoprazle with St. John’s Wort or rifampin; consult ritonavir-containing product information.
Use of strong CYP2C19 or CYP3A4 inhibitors (e.g. voriconazole) may result in increased exposure of lansoprazle. Refer to Voriconazole prescribing information</td></tr>
<tr><td>Omeprazole[6]</td><td>Time-dependent CYP2C19 inhibitor: May increase systemic exposure of co-administered CYP2C19 substrates.
Activity to increase intragastric pH may affects exposure of agents with pH-dependent solubility
Antiretrovirals (e.g. rilpivirine, atazanavir, nelfinavir):
<table>
<tr><td>Rilpivirine</td><td>AUC ↓ 40%</td><td>Cmax ↓40%</td><td>Cmin ↓ 33%</td></tr>
<tr><td>Nelfinavir</td><td>AUC ↓ 36%</td><td>Cmax ↓37%</td><td>Cmin ↓39%</td></tr>
<tr><td>Atazanavir</td><td>AUC ↓ 94%</td><td>Cmax ↓ 96%</td><td>Cmin ↓ 95%</td></tr>
<tr><td>Saquinavir/ritonavir</td><td>AUC↑ 82%</td><td>Cmax ↑ 75%</td><td>Cmin ↑ 106%</td></tr>
</table>

o Rilpivirine – concomitant use is contraindicated
o Atazanavir – see prescribing information
o Nelfinavir – avoid concomitant use
Saquinavir exposure may be increased with potential for toxicity
o See prescribing information monitor for potential toxicities

Cilostazol: Cmax increased 18%; AUC increased 26%. Cmax of active metabolite (4-7x cilostazol activity) increased 29%; AUC increased 69%
Citalopram (CYP2C19 substrate): Increased citalopram exposure, increasing the risk of QT prolongation. Limit the dose of citalopram to 20 mg daily
Clopidogrel (CYP2C19 substrate): Reduced exposure of clopidigrel active metabolite ~41-46% and platelet inhibition. Avoid concomitant therapy; consider alternative anti-platelet therapy.
Concomitant therapy with Clarithromycin/Amoxicillin: See clarithromycin prescribing information
Diazepam: Increased exposure of diazepam (e.g. IV administration (0.1 mg/kg) yielded 27% reduction in clearance and 36% increase in half-life). Monitor for sedation and consider dose reduction.
Digoxin: Bioavailability increased 10%. Monitor digoxin levels.
Drugs dependent on gastric pH for absorption (e.g iron salts, erlotinib, mycophenolate mofetel, ketoconazole): Absorption may be decreased.
Methotrexate: Serum levels of methotrexate and its metabolite may be increased and prolonged, increasing the risk of methotrexate toxicity. Consider withdrawal of omeprazole, especially with high-dose methotrexate therapy.
Mycophenolate mofetil: A reduction in exposure to the active metabolite (mycophenolic acid) may occur (Cmax reduced 52%; AUC reduced 23%). Clinical relevance not established. Use omeprazole with caution.
Phenytoin: May increase phenytoin exposure. Monitor phenytoin serum concentrations</td></tr>
</table>

Table 1. Labeled Drug Interactions Warnings for PPIs

Generic Name	Drug Interaction
	Tacrolimus: Potential for increased exposure, especially in transplant patients with intermediate/poor CYP2C19 metabolism. Consider TDM Voriconazole: Doubling of omeprazole exposure noted with concomitant voriconazole exposure (Cmax doubled, AUC increased 4-fold) Warfarin: Warfarin: Increased INR & PT; potential for abnormal bleeding and death; Monitor PT/INR **ENZYME INTERACTIONS** Use of strong CYP2C19 or CYP3A4 inducers (e.g. St. John's Wort, rifampin, Ritonavir-containing products) may result in decreased omeprazole exposure. Avoid concomitant use of St. John's Wort, rifampin and see consult prescribing information for ritonavir-containing products. Use of strong CYP2C19 or CYP3A4 inhibitors (e.g. voriconazole) may result in increased exposure of omeprazole. Dose reductions may be considered in patients receiving high doses of omeprazole (e.g. Zollinger-Ellison syndrome) **LABORATORY INTERACTIONS** In testing for neuroendocrine tumors, false positive chromogranin A (CgA) levels may result. Stop omeprazole 14 days prior and repeat test if positive result. In secretin stimulation tests, gastrin hypersecretion may result suggesting false positive for gastrinoma. Stop omeprazole 14 days prior to testing. In urine testing for THC, a false positive screening test may occur. Use alternative confirmatory methods to verify results.
Pantoprazole sodium[7]	Antiretrovirals: • Rilpivirine, Atazanavir, Nelfinavir exposure may be decreased, reducing antiviral effect and promoting the development of drug resistance o Rilpivirine – concomitant use is contraindicated o Atazanavir – see prescribing information o Nelfinavir – avoid concomitant use • Saquinavir exposure may be increased with potential for toxicity o See prescribing information monitor for potential toxicities • Other retrovirals: See prescribing information Clopidogrel: NO significant interaction Drugs dependent on gastric pH for absorption (e.g iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetel, ketoconazole/itraconazole): Absorption may be reduced. Use caution with mycophenolate mofetil in transplant patients as active metabolite exposure may be reduced (clinical relevance unknown) Methotrexate: May increase exposure of methotrexate (especially at high dose) and/or its metabolite with potential toxicities. Consider withdrawal of Protonix Warfarin: Increased INR & PT; potential for abnormal bleeding and death; Monitor PT/INR **ENZYME INTERACTIONS** Use of strong CYP2C19 or CYP3A4 inducers (e.g. St. John's Wort, rifampin, Ritonavir-containing products) may result in decreased pantoprazole exposure Use of strong CYP2C19 or CYP3A4 inhibitors (e.g. voriconazole) may result in increased exposure of pantoprazole **LABORATORY INTERACTIONS** In testing for neuroendocrine tumors, false positive chromogranin A (CgA) levels may result. Stop pantoprazole 14 days prior and repeat test if positive result. In urine testing for THC, a false positive screening test may occur. Use alternative confirmatory methods to verify results.

Table 1. Labeled Drug Interactions Warnings for PPIs

Generic Name	Drug Interaction
Rabeprazole sodium[8,9]	Antiretrovirals: • Rilpivirine, Atazanavir, Nelfinavir exposure may be decreased, reducing antiviral effect and promoting the development of drug resistance o Rilpivirine – concomitant use is contraindicated o Atazanavir – see prescribing information o Nelfinavir – avoid concomitant use • Saquinavir exposure may be increased with potential for toxicity o See prescribing information monitor for potential toxicities Digoxin: Potential increased digoxin exposure. Consider TDM Drugs dependent on gastric pH for absorption (e.g iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetel, ketoconazole/itraconazole): Absorption may be reduced. Use caution with mycophenolate mofetil in transplant patients as active metabolite exposure may be reduced (clinical relevance unknown) Methotrexate: May increase exposure of methotrexate and/or its metabolite with potential toxicities. Consider withdrawal of Aciphex Tacrolimus: Potential for increased exposure, especially in transplant patients with intermediate/poor CYP2C19 metabolism. Consider TDM Warfarin: Increased INR & PT; potential for abnormal bleeding and death **LABORATORY INTERACTIONS** In testing for neuroendocrine tumors, false positive chromogranin A (CgA) levels may result. Stop Aciphex 14 days prior and repeat test if positive result. In secretin stimulation tests, gastrin hypersecretion may result suggesting false positive for gastrinoma. Stop rabeprazole 14 days prior to testing. In urine testing for THC, a false positive screening test may occur. Use alternative confirmatory methods to verify results.

Abbreviations: TDM, therapeutic drug monitoring

Appendix E: Systematic Reviews

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
Yang 2017[41]	Searched Cochrane, Medline, and EMBASE from inception to August 2014 Selected RCTs including patients that required NSAID therapy and a PPI; studies comparing different PPIs were included where the primary outcome was ulcer complications (bleeding, perforation, obstruction) and/or endoscopic peptic ulcer rates	The aim of this study was to determine whether any one PPI is better at preventing NSAID-related ulcers Pairwise Meta-analysis Results **Endoscopic peptic ulcer**: No significant differences found • ESO vs. OME (1 study, 38 patients) RR 5.53 (0.28, 107.96); not significant • ESO vs. other PPIs (LAN, RAB, PAN); no studies identified • OME vs. PAN (1 study, 595 patients) RR 1.27(0.4, 3.99); not significant • OME vs other PPIs (LAN or RAB); no studies identified • LAN vs RAB or PAN; no studies identified • RAB vs PAN; no studies identified *Studies included adult patients* **Ulcer Complications:** No studies were found directly comparing the PPIs with this as a primary endpoint
Hu, 2017[39]	Searched Medline, Embase, Cochrane Library, ClinicalTrails.gov, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBM) to collect all RCTs up to May 1st, 2016. Included RCTs comparing PPIs in the treatment of duodenal ulcers in adults, with duodenal ulcers outcome diagnosed by endoscopy; patients should not have received other medical therapies before the trial, including compounds of ulcerogenic potential (e.g. NSAIDS, corticosteroids); used intention-to-treat (ITT) data for analysis.	Pairwise Meta-analysis Results **4 week duodenal ulcer healing rate**: No significant differences found • OME 20 vs. PAN 40 ; no significant difference • OME 20 vs. LAN 30; no significant difference • No other head-to-head studies found • Note that these comparison studies did no report on *H.pylori* status of the included patients

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
Li, 2017[28]	Searched PubMed, Embase, and the Cochrane library from inception to November 2016, as well as manually searched the reference lists of published systematic reviews. Titles/abstracts/full-text were screened by 2 investigators Included RCTs comparing FDA-approved PPIs for at least 4 weeks of continuous therapy in patients 18 years or older of with EE diagnosed/healing confirmed by endoscopic examination. Outcomes were 4 or 8-weeks and investigator assessed heartburn symptoms	Li et al performed a systematic review to identify all available PPI head-to-head trials so that they could then perform a network meta-analysis. Although their statistical network findings will not be included for our report since this is indirect observational type evidence, the list of available studies is useful to understand whether any more recent RCTs have been published with respect to the SRs, with direct evidence, included in our report.
Petryszyn, 2016[33]	*Article ultimately excluded since other included SRs were more robust and there appears to be selective reporting* Searched PubMed and EBSCO databases; search dates not specified; most recent RCT is dated 2007 Included studies comparing esomeprazole versus a different PPI for the treatment of GERD related disorders	**Erosive esophagitis healing at 4 and/or 8 weeks of treatment** • **ESO 40 vs. OME 20** (3 studies; missing Kao 2003 found by SR McDonagh et al, 2009); MA, random-effects estimates showed a significant difference in favor of ESO at 4 weeks (0.74, CI 0.59 to 0.94) and at 8 weeks (0.61 CI 0.41 to 0.9) • **ESO 40 vs. PAN 40** (1 study) and ESO 40 vs. LAN 30 (1 study); both studies individually showed significantly more healed patients in the ESO group versus the comparator at 8 weeks. Nonetheless, this evidence is based on only one study for each comparison, *whereas, the authors McDonagh et al, 2009, found more studies and arrive at a different conclusion with meta-analysis.* • **ESO 40 vs. LAN 30:** *authors selectively report findings* from only one RCT (Castell et al), although they mention briefly also finding (Zheng et al). Moreover, other SRs by McDonagh et al and by Wu et al have searches that appear more robust as they found more studies for this comparison **Maintenance GERD therapy after 6 months (relapse prevention)** • ESO 20 vs. PAN 20; authors found two conflicting studies, however their pairwise MA, random effects estimate showed no significant difference between interventions. **Non-erosive esophagitis** • ESO 40 vs. OME 20; only 1 study was identified showing comparable efficacy in the resolution of heartburn rate after 4-weeks of treatment.

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
Mei, 2016[30]	Searched PubMed, EMBASE and Cochrane up to December 2014 Included RCTs of GERD patients comparing ESO with any other PPI for maintenance therapy lasting at least 6 months	**Relapse rate comparison during 6 months treatment** • ESO 20 vs. LAN 15: authors identified two RCTs both which individually showed a significant difference in favor or ESO o RCT Lauritsen et al effect estimate (0.66 [95% CI 0.53 to 0.84]) in favor of ESO o RCT Devault et al effect estimate (0.61 [95% CI 0.47 to 0.81]) in favor of ESO • ESO 20 vs. PAN 20: authors found two conflicting studies *Studies included adult patients*
NICE Guideline for Pediatric GERD, 2015[26]	Search was conducted in Medline up to April 2014 (per Appendix F, search F.9 of publication) Regarding treatment, the highest possible evidence level in patients <18 years of age with GERD, were well-conducted systematic reviews, meta-analysis of RCTs, or individual RCTs that were selected.	*No direct head-to-head evidence was found comparing PPIs*
Zeng, 2015[40]	Searched CHKD, VIP, China Info, the National Digital Library of China, Google Scholar, PubMed, Lippincott Williams & Wilkins, and the Wiley Online Library up to September 10, 2014, for studies comparing Lansoprazole and Omeprazole in patients with duodenal ulcer who reported a formalized healing and eradication rates for duodenal ulcer.	• 9 randomized controlled trials were included • Meta-analysis resulted in no significant differences between lansoprazole and omeprazole containing regimens with respect to duodenal ulcer healing rate • Authors report H.pylori eradication rates, however, they do not describe the full details of the treatment arms among the trials included (e.g. drug doses, duration). There is not enough information to determine which of these studies, if any, examine modern treatment regimens.
Teng, 2015[34]	Searched PubMed and Cochrane Library up to Feb 2015 Included head-to-head RCTs comparing oral esomeprazole with omeprazole for the treatment of GERDor peptic ulcer disease. Participants were adults with GERD, peptic ulcer disease or H. pylori infection. Outcomes of interest included resolution of GERD-related symptoms, esophagitis healing, peptic ulcer	Authors found 7 studies related to GERD, 0 related to peptic ulcer disease, and 8 related to H.pylori infection • Meta-analysis calculations used random effect model **GERD** **Endoscopy positive reflux esophagitis** **Healing rates at week 4 and 8** • ESO 40 vs. OME 20: *Week 4*: The relative risk of ESO 40 versus OME 20 was 1.13 (95% CI 1.04 to 1.22) in favor of ESO and the corresponding NNT was 12 (3 studies)

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
Teng, 2015[34] *continued*	healing, H. pylori eradication, quality of life andadverse effects.	*Week 8*: The relative risk of ESO 40 versus OME 20 was 1.07 (95% CI 1.02 to 1.12) in favor of ESO and the corresponding NNT was 17 (5 studies) • ESO 20 vs. OME 20: *Week 4*: no significant difference (1 study) *Week 8*: The relative risk of ESO 20 versus OME 20 was 1.04 (95% CI 1.01 to 1.08) in favor of ESO and the corresponding NNT was 30 (2 studies) • Overall: ESO 40 or 20 vs. OME 20: Significant difference in favor of ESO at 4 and 8 weeks. **Endoscopy negative reflux esophagiti**s Resolution of heartburn symptoms at week 4 • ESO 40 vs. OME 20: no significant difference in heartburn resolution (defined as no heartburn episodes during the previous seven consecutive days) at week 4 **H.pylori Eradication** • Treatments were 7-day triple therapy regimens with either PPI /amoxicillin/clarithromycin OR PPI/metronidazole/clarithromycin H.pylori eradication rates as assessed by histology and urea breath test at 4 to 8 weeks • ESO 40 vs. OME 20 (2 studies) The relative risk of ESO 40 versus OME 20 was 1.17 (95% CI 1.01 to 1.32) in favor of ESO • ESO 20 vs. OME 20 (5 studies): no significant difference • Overall: ESO 40 or 20 vs. OME 20: No significant difference
Qi, 2015[36]	Searched PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov databases were carried out for reports up to Feb. 28, 2015 Selected RCTs in adult patients compared the effectiveness or tolerability of esomeprazole and omeprazole. Outcomes of interest were (i) endoscopic healing rate as the primary outcome; (ii) relief of symptoms, wherein heartburn, regurgitation, or other GERD-related symptoms were well controlled or relieved as the second	Random effects model was used for meta-analysis of efficacy endpoints, while a fixed effects model was used for the tolerability outcome **GERD Endoscopic healing rate at 8 weeks** 6 studies included • Overall, there was a significant difference between ESO vs. OME (RR = 1.06, 95% CI [1.01, 1.10], I2 = 72%, p = 0.01) • ESO 40 vs OME 20: There was a significant difference between esomeprazole 40 mg and omeprazole 20 mg (RR = 1.07, 95% CI [1.004, 1.14], I2 = 78%, p = 0.04) • ESO 20 vs. OME 20: there was no significant difference (RR = 1.04, 95% CI [0.999, 1.07], I2 =

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
	outcome of effectiveness; and (iii) tolerability, defined as discontinued from a study during therapy for any reason.	0%, p = 0.05) by subgroup according to dosage of ESO 20 **Symptom relief determined by subjective patient evaluation** • ESO 20 or 40 vs. OME 20: no significant differences were found based on 7 studies included; moreover, no differences were found by subgroup according to the esomeprazole dosage. • ESO 20 vs. OME 40: Based on 1 study evaluating on-demand therapy OME 40 was significantly better than ESO 20 **Tolerability** • ESO vs. OME: no significant difference were found overall or by any subgroup according to dose of each agent
NICE Clinical Guideline for adult GERD, 2014[45]	Searched Medline up to September 2012 Included systematic reviews/meta-analysis, RCTs, quasi-RCTs comparing PPI treatments vs. placebo and one another with >30-days follow-up period. Outcomes of interest included the following : endoscopic appearance/chance in LA grade/resolution of oesophagitis; health related QOL scales; acid exposure time; progression to Barrett's oesophagus or carcinoma; adverse events (headache, diarrhoea, nausea, drug interactions, metallic taste, rash) mortality; hypergastroanaemia	*From Appendix F in the NICE report (1.2.1.7.2)* *Full-dose PPI versus full-dose PPI* **ESO 40 vs. LAN 30** • Pooled-effect estimate (from 2 studies) showed a significant difference in EE healing at week 8 for LA grades C and D in favor of ESO, however, authors judge the quality of one trial to be low *Low-dose PPI versus low-dose PPI* **ESO 20 vs. OME 20** • Pooled-effect estimate (from 2 studies) resulted in no significant difference in EE healing at week 8 for LA grades C and D "The GDG noted that the treatments that provided best expected value for money (highest mean net monetary benefit in probabilistic analysis) were all PPIs given at what would conventionally be considered a 'full' dose (esomeprazole 40 mg/day, pantoprazole 40 mg/day, rabeprazole 20 mg/day) or higher (rabeprazole ER 50 mg/day)." "As for the healing phase, the GDG felt it would not be appropriate to recommend a particular PPI in view of the uncertainty in the evidence." "Although the GDG could not confidently determine which PPI was the most clinically effective, it was confident that

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
		PPIs in general were efficacious for treating severe erosive reflux disease."
Xia, 2013[38]	Searched Medline, Embase, and Web of Science to December 2012; and the Cochrane Central Register of Controlled Trials (issue 12, 2012) Included RCTs involving adults and comparing RAB 20 once daily with OME 20 once daily for maintenance therapy lasting up to 8 weeks. Outcomes of interest were (1) healing of erosive GERD endoscopically using Hetzel-Dent (HD), Savary-Miller (SM), and Los Angeles (LA) classifications; and (2) symptomatic relief of erosive GERD	6 RCTs containing 1,895 patients were eligible. **RAB 20 vs. OME 20** **Endoscopic relief rates**: no difference was found with treatment in trials out to 8 weeks. **Heartburn relief rates:** A significant difference was found between the two groups for 8-week treatment trials, in favor of rabeprazole: Rabeprazole 20 vs. Omeprazole 20m once (RR = 1.133; 95% CI: 1.028–1.249; P = 0.012), however there was considerable heterogeneity ($I2$ = 72.9%, P = 0.011). Authors note that publication bias was not observed (Egger test, P = 0.060). **Adverse events**: no significant difference found with 8-week treatment trials.
Wu, 2013[27]	Searched Medline, Embase, Cochrane Library, and scanned reference list of papers (search date are not provided by the authors in full text or in supplement) Nonetheless a recent systematic review for a network meta-analysis by Li et al, 2017, did not reveal any additional DEX vs. other PPI RCTs not addressed by Wu et al.[28] Li et al search included PubMed, Embase, and the Cochrane library from inception to November 2016.[28] Included RCTs comparing dexlansoprazole or esomeprazole with a common comparator, which could be placebo or another PPI drug. The patient population was patients with GERD (including EE or non-erosive esophagitis). Reported the outcomes of interest were related to healing data.	Pair-wise direct meta-analysis (Mantel-Haenszel random-effects) **DEX 60 vs. LAN 30** • No significant differences found in 8 week healing rates for EE of Los Angeles grades A-D at baseline or for high-grade EE at baseline (Los Angeles grades C and D). **ESO 40 vs. LAN 30** • No significant differences found in 8 week healing rates for EE of Los Angeles grades A-D at baseline or for high-grade EE at baseline (Los Angeles grades C and D).

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
McDonagh, 2009[29]	Searched the Cochrane Library (4th Quarter 2008), Medline (1966- week 2 of November 2008), Embase (1980-3rd Quarter 2004), and reference lists of review articles Included English-language RCTs of at least 4 weeks' duration in adult outpatients with symptoms of GERD, peptic ulcer, or NSAID-induced ulcer. Included interventions were PPIs (OME, ESO, LAN, PAN, RAB) compared to another PPI. For adverse effects, we also included observational studies. Outcomes measured were symptoms, functional outcomes, endoscopic healing, eradication of *H.pylori*, quality of life, and adverse effects	**Comparative evidence for erosive and non-erosive GERD** **GERD Symptom Relief in Patients with EE** (Random effects modeling): • At comparable doses, no significant differences in symptom relief of esophagitis were identified between PPIs, with the exception of a significant difference found between ESO 40mg/d and OME 20 mg/d on the outcome of complete symptom relief at 4 weeks [pooled risk difference from 4 trials was 8% (95% CI 3 to 13), and a number needed to treat of 13]. No difference was found for ESO 20 vs OME 20 however (1 trial). • Pooled estimates from 5 other head-to-head trials included showed no significant difference between other PPI comparisons for symptom resolution at 4 weeks [ESO 40 vs. LAN 30 or PAN 40] • 7 head-to-head studies identified found no significant differences for PPI comparisons including (1) LAN 30 vs. OME 20, OME 40, or PAN 40; (2) OME 20 vs. PAN 20, PAN 40, or RAB 20 and (3) OME 40 vs. PAN 40 with respect to resolution of symptoms at 4 weeks **Healing of esophagitis** (Random effects modeling): • 13 studies showed no difference between OME, LAN, PAN, and RAB for healing of esophagitis at 4 and 8 weeks. • Pooled analysis for 4- and 8-week healing rates from 4 trials showed a significant difference in favor of ESO 40 mg/d compared to OME 20 mg/d; risk difference 7% (95% CI 1 to 12) with a number needed to treat of 14, and risk difference of 5% (95% CI 1 to 9) with number needed to treat of 20, respectively. • Pooled analysis for 4- and 8-week healing rates from 3 trials showed a significant difference in favor of ESO 40 mg/d compared to LAN 30 mg/d; risk difference 5% (95% CI 2 to 7) and risk difference of 3% (95% CI 1 to 5), respectively. • Pooled analysis for 4-week healing rates (but not 8 week healing rates) from 3 trials showed a significant difference in favor of ESO 40 mg/d compared to PAN 40 mg/d; risk difference 5% (95% CI 2 to 8)

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
McDonagh, 2009[29] *continued*		

Difference in healing of esophagitis rates at 4 and 8 weeks in the percent of patients classified as healed in each arm (Random effects modeling)

Comparators (mg/d)	4 weeks: D, 95% CI	8 weeks RD, 95% CI
ESO 20 vs. OME 20 (2 studies)	No difference	No difference
ESO 40 vs. OME 20 (4 and 5 studies respectively)	7% (1 to 12) Favoring ESO	5% (1 to 9) Favoring ESO
LAN 30 vs. OME 20 (3 studies)	No difference	No difference
PAN 20 vs. OME 20 (1 study)	No difference	No difference
PAN 40 vs. OME 20 (1 study)	No difference	No difference
RAB 10 vs. OME 20 (1 study)	No difference	No difference
RAB 20 vs. OME 20 (2 studies)	No difference	No difference
LAN 30 vs. OME 40 (1 study)	No difference	No difference
PAN 40 vs. OME 40 (1 study)	No difference	-
PAN 40 vs. LAN 30 (1 study)	No difference	No difference
ESO 40 vs. LAN 30 (3 studies)	5% (1 to 9) Favoring ESO	No difference; however when using fixed effects modeling, a significant difference results, 3% (1 to 5), favoring ESO
ESO 40 vs. PAN 40 (4 studies)	5% (2 to 8) Favoring ESO	No difference

Healing in moderate to severe (Grades C/D or 3/4) erosive esophagitis:

- No significant differences found for ESO 20 vs. OME 20 (2studies) or for LAN 30 vs. OME 20 (2 studies)
- Pooled risk difference from 3 studies favored ESO 40mg/d versus OME 20 mg/d (16% at 4 weeks and 13% at 8 weeks; number needed to treat = 6 at 4 weeks, 8 at 8 weeks).
- Pooled risk difference from 2 studies favored ESO 40 vs. LAN 30 (8% at 4 weeks and 9% at 8 weeks; number needed to treat = 13 at 4 weeks, 11 at 8 weeks)
- Evidence was mixed on differences between ESO 40 vs. PAN 40. At 4 weeks, ESO 40 mg had a higher healing rate than PAN 40 mg; pooled risk difference (2 studies) 14% (95% CI 7 to 20). At 8 weeks, no difference was found in a single small study of patients with mild to moderate esophagitis.

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
McDonagh, 2009[29] *continued*		**Prevention of relapse in patients with erosive esophagitis** • For maintenance of healed esophagitis, there was good evidence that no difference exists between OME, LAN, and RAB. • Authors found 2 RCTs (Lauritsen el al[31] and Davault et al[32]) found lower relapse rates for esomeprazole 20 mg than for lansoprazole 15 mg o RCT by Lauritsen el al[31] : relapse rates at 6 month (83% [95% CI, 80–86%] of esomeprazole recipients vs. 74% [95% CI, 70–78%] of lansoprazole recipients; P < 0.0001[31] o RCT by Davault et al: remission rates at 6 months (84.8% compared with 75.9%; P=0.0007), in favor of ESO • There are mixed findings for the difference in maintaining symptomatic and endoscopic remission at 6 months, for ESO 20 versus PAN 20, however, the dose of pantoprazole at 20mg per day is lower than the approved dosing for this indication. **Symptom relief in patients with non-erosive GERD:** • 3 head-to-head trials in patients with GERD, without erosive esophagitis on endoscopy, found no difference between ESO 20 mg/d versus OME 20 mg/d, PAN 20 mg/d, or RAB 10 mg/d. • Authors also found indirect evidence suggesting similar efficacy for heartburn resolution and complete symptom relief for all 5 PPIs **Evidence in children:** no direct head-to-head comparison RCTs for reflux esophagitis in children were found **Comparative effectiveness in treating patients with peptic ulcer and NSAID-induced ulcer** **Duodenal ulcer** • For healing of duodenal ulcer at 4 weeks, 5 trials were pooled comparing OME 20 vs. LAN 30 and 1 trial each comparing OME 20 vs. PAN 40, and RAB 20; and OME 40 vs. ESO 40. No significant difference were found between these comparisons • 1 trial was identified addressed maintenance, comparing LAN 15 and 30 vs. OME 20 for up to 12 months. There were no significant differences at 6 and 12 months. • Authors concluded that there was strong evidence for OME and LAN having similar effectiveness in both symptom relief and endoscopically verified healing. The pooled risk difference for 5 trials showed a non-significant difference. • "Symptom relief was an important measure in ulcer disease and did not always correlate with healing confirmed by endoscopy."

Table 1. Systematic Reviews with Efficacy Outcomes

Study lead author, year	Methods	Results
McDonagh, 2009[29] *continued*		**Gastric ulcer** • OME 20 vs. RAB (3 studies): no significant difference in healing rates was found. • Based on one RCT, symptom relief was better with rabeprazole 20 mg than omeprazole 20 mg in 3 of 12 individual measures at 3 weeks and in 2 measures at 6 weeks but overall, there was no difference in change in well-being or in antacid use. • Overall no difference in symptom relief was found between rabeprazole 10 mg and omeprazole 20 mg daily. **Nonsteroidal anti-inflammatory drug-induced ulcer** • There were no head-to-head trials. **Comparative effectiveness in preventing NSAID-induced ulcer** • 1 trial was identified where PAN 20 and 40 were compared to OME 20 and did not indicate statistically significant differences in rates of therapeutic or endoscopic failure at 6 months in a group of patients taking nonsteroidal anti-inflammatory drugs regularly for arthritic conditions.[55] Therapeutic failure was defined as peptic ulcer, >10 erosions, reflux esophagitis, and discontinuations of study drug due to an adverse event or severe gastrointestinal symptoms.

Abbreviations: DEX, dexlansoprazole; DR, delayed release; EE, erosive esophagitis; ESO, esomeprazole; GERD, gastroesophageal reflux disease; LAN, lansoprazole; MA, meta-analysis; OME, omeprazole; PAN, pantoprazole; RAB, rabeprazole

Table 2. Systematic Reviews with Safety Outcomes

Study lead author, year	Methods	Results
Niu, 2017[42]	Searched Cochrane, Medline, and EMBASE for published titles up to February 2015 Selected published RCTs and non-randomized controlled trials of patients with or without PPIs in addition to clopidogrel for coronary artery disease. Studies must have had the incidence of MACE (major adverse cardiovascular events) in patients with coronary artery disease as primary or secondary end point.	**Risk of major adverse cardiovascular events** (**MACE**; including cardiovascular death, nonfatal myocardial infarction, stroke, stent thrombosis, and revascularization) • Combination therapy with PPIs and clopidogrel increased risk of MACEs (OR: 1.42; 95% confidence interval [CI]: 1.30-1.55), especially in rapid metabolizers of CYP2C19 (OR: 1.42; 95% CI: 1.12-1.81), but not in decreased metabolizers. • There was a similar increased risk of MACEs among the following PPIs omeprazole, lansoprazole, esomeprazole, and pantoprazole; rabeprazole, however, was not associated with increased risk of MACE (OR: 1.03; 95% CI: 0.55-1.95).
Mei, 2016[30]	Searched PubMed, EMBASE and Cochrane up to December 2014 Included RCTs of GERD patients comparing ESO with any other PPI for maintenance therapy lasting at least 6 months	**Drug-related adverse event outcomes—** Authors found two studies including this outcome, one comparing ESO 20 vs. LAN 15, and another comparing ESO 20 vs. PAN 20. No significant differences were found for either comparison
Teng, 2015[34]	Searched PubMed and Cochrane Library up to Feb 2015 Included head-to-head RCTs comparing oral esomeprazole with omeprazole for the treatment of GERDor peptic ulcer disease. Participants were adults with GERD, peptic ulcer disease or H. pylori infection. Outcomes of interest included resolution of GERD-related symptoms, esophagitis healing, peptic ulcer healing, H. pylori eradication, quality of life andadverse effects.	Authors found 7 studies related to GERD, 0 related to peptic ulcer disease, and 8 related to H.pylori infection • Meta-analysis calculations used random effect model **Treatment-associated adverse effects: abdominal pain, diarrhea, flatulence, and headache** ***ESO vs. OME*** • Authors state that upon pooling data on adverse effects from all the included studies accounting for a total of 9200 patients, the safety profiles of esomeprazole and omeprazole were similar. There were no significant differences in the pooled estimates of the treatment-associated adverse effects for ESO versus OME with respect to abdominal pain, diarrhea, flatulence, and headache.

Table 2. Systematic Reviews with Safety Outcomes

Study lead author, year	Methods	Results
Qi, 2015[36]	Searched PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov databases were carried out for reports up to Feb. 28, 2015 Selected RCTs in adult patients compared the effectiveness or tolerability of esomeprazole and omeprazole. Outcomes of interest were tolerability, defined as discontinued from a study during therapy for any reason and other efficacy outcomes as described in the previous table	**Tolerability:** defined as discontinued from a study during therapy for any reason ***ESO vs. OME***: fixed-effects meta-analysis showed no significant difference between treatment drugs overall or by any subgroup according to dose of each agent
Xia, 2013[38]	Searched Medline, Embase, and Web of Science to December 2012; and the Cochrane Central Register of Controlled Trials (issue 12, 2012) Included RCTs involving adults and comparing RAB 20 once daily with OME 20 once daily for maintenance therapy lasting up to 8 weeks. Outcomes of interest were (1) healing of erosive GERD endoscopically using Hetzel-Dent (HD), Savary-Miller (SM), and Los Angeles (LA) classifications; and (2) symptomatic relief of erosive GERD	6 RCTs containing 1,895 patients were eligible. **RAB 20 vs. OME 20** **Adverse events**: meta-analysis showed no significant difference in adverse events, upon analyzing trials with 8-weeks of treatment.
McDonagh, 2009[29]	Searched the Cochrane Library (4th Quarter 2008), Medline (1966- week 2 of November 2008), Embase (1980-3rd Quarter 2004), and reference lists of review articles Included English-language RCTs of at least 4 weeks' duration in adult outpatients with	**Long-term studies in patients with GERD (lasting 6 months or longer):** there was no significant difference found in the number of adverse events or number of withdrawals due to adverse events for certain PPI comparisons: LAN vs. OME, RAB vs. OME, or ESO vs. PAN **Short term studies in patients with GERD**: "The proportion of patients withdrawing due to adverse events in these studies was very low, with most studies reporting 1% to 3%. No study found significant differences among treatment groups in the rate of

Table 2. Systematic Reviews with Safety Outcomes

Study lead author, year	Methods	Results
	symptoms of GERD, peptic ulcer, or NSAID-induced ulcer. Included interventions were PPIs (OME, ESO, LAN, PAN, RAB) compared to another PPI. For adverse effects, we also included observational studies. Outcomes measured were symptoms, functional outcomes, endoscopic healing, eradication of *H.pylori*, quality of life, and adverse effects	withdrawals for adverse effects. Reports of serious adverse events were uncommon and generally balanced among the drugs. Many of these incidences could be associated with preexisting diseases."[29]

Abbreviations: DEX, dexlansoprazole; DR, delayed release; EE, erosive esophagitis; ESO, esomeprazole; GERD, gastroesophageal reflux disease; LAN, lansoprazole; MA, meta-analysis; OME, omeprazole; PAN, pantoprazole; RAB, rabeprazole

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6. Prilosec (omeprazole) delayed-release capsules and Prilosec (omeprazole magnesium) for delayed-release oral suspension [package insert]. Wilmingon, DE. AstraZeneca. Revised December 2016.
7. Protonix (pantoprazole sodium) delayed release tablets and suspension [package insert]. Konstanz, Germany. Takeda GmbH, Pfizer. Revised December 2017.
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