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Proton Pump Inhibitors and Histamine-2 Receptor Antagonists Class Updates with New Drug Evaluation

Date of Review: August 2024

Date of Last Review: October 2020
Dates of Literature Search: 01/01/2020 – 04/08/2024

Generic Name: vonoprazan

Brand Name (Manufacturer): Voquezna® (Phathom)
Dossier Received: No

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update: The purpose of this update is to evaluate new evidence for proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) for the treatment of peptic ulcer disease (PUD), gastrointestinal esophageal reflux disease (GERD), erosive esophagitis, Zollinger-Ellison Syndrome, and non-steroidal anti-inflammatory drug (NSAID)-induced ulcers. The safety and efficacy of vonoprazan (VOQUEZNA), a new potassium-competitive acid blocker (PCAB) for treatment of erosive esophagitis, will also be reviewed. Evidence for the management of *Helicobacter pylori (H. pylori)* infections with PPIs, H2RAs, and PCABs will be reviewed in a separate class update.

Plain Language Summary:

- The esophagus carries food from the mouth to the stomach. Gastroesophageal reflux disease (GERD) occurs when stomach acid flows back into the esophagus and causes symptoms including heartburn, backwash of undigested food or sour liquid, stomach pain, nausea, vomiting, trouble swallowing, unexplained cough, sore throat, or hoarseness due to irritation of the vocal cords.
- Many people can manage the discomfort of acid reflux with lifestyle changes. Avoiding foods that make the symptoms worse (i.e. fatty foods, chocolate, caffeine, peppermint), reducing alcohol intake, quitting cigarettes, and losing weight can all improve symptoms of GERD. If acid reflux does not improve with these changes, an over-the-counter antacid may be tried. There are 2 types of prescription acid blockers: histamine receptor antagonists and proton pump inhibitors. Histamine receptor antagonists are started when people have mild GERD symptoms. For people with severe symptoms that do not improve with histamine receptor antagonists, a proton pump inhibitor may be started.
- Proton pump inhibitors are usually effective in healing the damage caused by GERD when taken for 8 weeks. Long-term use of proton pump inhibitors may increase the risk of hip, wrist and spine fractures, diarrhea due to certain infections, and keeps the body from absorbing enough minerals and vitamins from foods. For these reasons, treatment is usually limited to 8 weeks for GERD.
- A new type of medicine, vonoprazan (VOQUENZA), called a potassium-competitive acid blocker, was recently approved by the U.S. Food and Drug Administration (FDA) to help people with severe form of GERD called erosive esophagitis. In a clinical trial, vonoprazan was not less effective than a proton pump inhibitor in healing erosive esophagitis.

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- Side effects of vonoprazan include diarrhea, nausea, stomach bloating and pain, high blood pressure, and urinary tract infections. Some medicines should not be taken with vonoprazan, so it is important to ask your provider or pharmacist to check for drug interactions when starting treatment with vonoprazan.
- The Oregon Health Plan (OHP) has some proton pump inhibitors and histamine receptor antagonists designated as *preferred* on the Fee-For-Service (FFS) Preferred Drug List (PDL). Treatment with proton pump inhibitors for GERD is limited to 8 weeks because of serious side effects with long-term use.
- It is recommended that a prescriber send in documentation why a person needs vonoprazan before approving its use in OHP FFS patients. This process is called *prior authorization*.

Research Questions:

1. What is the comparative efficacy and safety of PPIs in the treatment of PUD, GERD, Zollinger-Ellison syndrome, and NSAID-induced ulcers?
2. What is the comparative efficacy and safety of H2RAs in the treatment of GERD?
3. What is the evidence for the safety and efficacy of vonoprazan to treat erosive esophagitis?
4. Are there populations based on demographic characteristics (e.g., age, race, ethnicity, co-morbidities, etc.) in which a PPI, H2RA, or vonoprazan may be more effective or cause more harm when used to treat PUD, GERD, Zollinger-Ellison syndrome, or NSAID-induced ulcers?

Conclusions:

- Two new systematic reviews[1,2] and one new clinical guideline[3] have been published since the Pharmacy and Therapeutics (P&T) Committee last reviewed these drug classes.
- There is no new evidence that evaluated the comparative safety and efficacy of PPIs with H2RAs in adults with acid-related gastrointestinal (GI) conditions. However, a 2023 systematic review assessed the effects of pharmacological treatments (PPIs, H2RAs, prokinetics, and alginates) for management of GERD in infants and children.[1] In infants, 2 studies did not show evidence for omeprazole or esomeprazole at resolving GERD symptoms over 2 weeks (very-low certainty of evidence).[1] Omeprazole and ranitidine may result in similar symptomatic improvement in infants based on a weekly gastro-esophageal reflux score over 2 weeks (very low-certainty evidence).[1] Two studies compared different doses of a single PPI (pantoprazole and rabeprazole) in children aged 1 year and older and found that they may provide little to no symptomatic and endoscopic benefit in children (very-low certainty of evidence).[1] No robust data in this population exist for other medications.[1] Further studies of these medications in pediatric patients with longer follow-up are needed.[1]
- There is conflicting evidence whether acid reflux triggers asthma.[2] A 2021 systematic review assessed the effectiveness of GERD treatment at improving asthma in adults and children.[2] The review did not find evidence that GERD treatment reduces severe exacerbations of asthma in adults (low-certainty evidence).[2] GERD treatment mildly improved forced expiratory volume in one second (FEV_1) in adults (mean difference [MD], 0.10 L, 95% confidence interval [CI], 0.05 to 0.15; moderate-certainty evidence) as well as reduced use of rescue asthma medications (MD, -0.71 puffs per day, 95% CI, -1.20 to -0.22; moderate-certainty evidence).[2] However, these improvements are not clinically meaningful.[2] There was not enough evidence to evaluate the effectiveness of GERD treatment in children, as only 2 studies included pediatric patients.[2]
- The American College of Gastroenterology (ACG) updated guidance for management of GERD in 2022.[3] Recommendations graded by ACG as *Strong* based on moderate-to high-quality evidence include:
    - 8-week trial of once daily PPI to empirically treat classic GERD symptoms of heartburn and regurgitation in people without alarming symptoms (strong recommendation; moderate-quality evidence).[3]
    - Treatment with PPIs over treatment with H2RAs for healing erosive esophagitis (strong recommendation; high-quality evidence).[3]
    - Treatment with PPIs over treatment with H2RAs for maintenance of healing for erosive esophagitis (strong recommendation; moderate-quality evidence).[3]

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- Since the previous drug class update, labeling for dexlansoprazole was updated to reflect the risk of heart valve thickening in pediatric patients less than two years of age.[4] Labeling for all PPIs was update to include potential safety risks for acute tubulointerstitial nephritis and severe cutaneous adverse reactions.[5] If either of these adverse effects occur, PPI therapy should be discontinued.[5] The rare adverse effect of hypomagnesemia has been reported with prolonged PPI treatment.[5] Refer to **Table 2** for additional details about recent FDA PPI safety warnings.
- The PCAB vonoprazan was approved by the FDA in November 2023 for healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.[6] The vonoprazan prescribing information recommends 20 mg once a day over 8 weeks for healing of erosive esophagitis and up to 24 weeks of 10 mg daily to maintain healing of erosive esophagitis.[6]
- A single phase 3, active-controlled, double-blind randomized controlled trial (RCT) of 1024 adult patients with endoscopically confirmed erosive esophagitis provided the evidence for FDA approval of vonoprazan.[7] During the initial 8-week healing phase, patients were randomized 1:1 to receive vonoprazan 20 mg once a day or lansoprazole 30 mg once a day.[7] The primary endpoint was percentage of patients with endoscopically confirmed healing of all grades of erosive esophagitis by week 8 in a noninferiority comparison (noninferiority margin, less than 10%).[7] Vonoprazan was noninferior to lansoprazole in the primary analysis of healing in the modified intention to treat (mITT) population (92.9% vs. 84.6%; difference, 8.3%; 95% CI, 4.5 to 12.2; low quality evidence).[7]
- Patients who showed endoscopically confirmed healed erosive esophagitis at Week 8 were re-randomized 1:1:1 into a 24-week maintenance phase to receive either vonoprazan 10 mg once daily, vonoprazan 20 mg once daily, or lansoprazole 15 mg once daily.[7] Maintenance of esophagitis healing and resolution of heartburn symptoms were evaluated over 24 weeks, and assessed in a noninferiority comparison.[7] Among 878 patients in the 24-week maintenance phase, vonoprazan was noninferior to lansoprazole in the analysis of erosive esophagitis healing in the mITT population (vonoprazan 20 mg vs. lansoprazole 15 mg: difference, 8.7%; 95% CI, 1.8 to 15.5 and vonoprazan 10 mg vs. lansoprazole 15 mg: difference, 7.2%; 95% CI, 0.2 to 14.1; low quality evidence).[7]
- The most common adverse events reported in the 8-week healing phase were gastritis, diarrhea, nausea, and stomach pain.[6] In the 24-week maintenance phase patients also reported hypertension and upper urinary tract infections.[6]
- Results of this phase 3 vonoprazan trial are not generalizable to adults that are *H. pylori* positive. In addition, most of the adults enrolled in this study were White, limiting the generalizability to real world populations.[7]

Recommendations:

- Maintain vonoprazan as non-preferred on the Preferred Drug List (PDL) with prior authorization criteria (see **Appendix 5**). No other changes to the PDL are recommended based on clinical evidence.
- Review PPI and H2RA costs in executive session.

Summary of Prior Reviews and Current Policy

- Previous reviews have demonstrated no clinically significant differences in efficacy or safety between the PPIs. There is insufficient evidence of efficacy and safety differences between H2RAs.
- A drug class update focused on PPIs and H2Ras was presented to the P&T Committee in October 2020. Evidence presented to the Committee supported Oregon Health Authority (OHA) policy, including treatment durations for PPI and H2RA therapies.[8]
- Coverage duration of PPI therapy for GERD is limited to 8 weeks due to long-term safety concerns associated with PPI treatment. Clinical PA criteria for *H-pylori* therapy is limited to 2 weeks but other funded conditions may be covered for up to 1 year (**Appendix 5**).

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- In the first quarter of 2024 (January through May), most of the utilization of H2RAs was for the preferred famotidine tablets. The preferred PPIs omeprazole and pantoprazole comprised most of the utilization for the PPI class.

Background:
Symptoms of GERD include heartburn and regurgitation of undigested food and stomach acid into the esophagus.[9] GERD is one of the most common disorders of the GI tract.[10] There is considerable geographical variation of GERD, with the general prevalence in North America ranging from 18% to 28%.[9] The most common complication of GERD is erosive esophagitis, estimated to occur in 25% to 50% of patients with GERD.[11,12] Extraesophageal manifestations of GERD may include laryngitis, pharyngitis and exacerbation of asthma.[9] Complications from GERD include Barrett's esophagus, esophageal stricture, and adenocarcinoma.[9]

There is no gold standard for the diagnosis of GERD.[3] The diagnosis is based on a combination of symptom presentation, endoscopic evaluation of esophageal mucosa, reflux monitoring, and response to therapeutic interventions.[3] Current therapies to treat GERD, PUD, and other acid-related GI diseases either prevent stimulation of the gastric parietal cell (e.g., H2RAs) or inhibit the gastric hydrogen-potassium-adenosine triphosphate (ATP)ase pump to reduce acid secretion (e.g., PPIs).[13,14] Overall, PPIs are reported to be more effective than H2RAs for resolution of symptoms associated with GERD and to improve healing of esophagitis.[14,15]

Treatment recommendations for GERD depend upon the frequency and severity of symptoms.[8] NICE guidance from 2019 recommends full-dose PPI therapy in adults for 8 weeks to heal severe esophagitis.[8] For adults using NSAIDs with diagnosed peptic ulcer, NICE guidance recommends discontinuing the use of NSAIDs where possible, and offering full-dose PPI or H2RA therapy for 8 weeks.[8] Although PPIs are effective for healing erosive esophagitis, some patients do not achieve success with PPI treatment.[16,17] Inadequate healing of erosive esophagitis after 8 weeks of PPI therapy can be expected in 5% to 20% of patients,[18] with rates up to 30% reported in patients with severe esophagitis.[19] After healing, recurrence over 12 months occurs in 10% to 45% of patients despite PPI therapy, with the higher rates associated with severe baseline esophagitis.[18]

The PCABs inhibit acid secretion by competitively blocking the potassium exchange channel of the hydrogen-potassium ATPase pump and inhibiting gastric acid secretion.[13] Vonoprazan is a new PCAB recently approved by the FDA to promote and maintain healing of erosive eophagitis.[6] Vonoprazan and another PCAB, tegoprazan, have been in use in Asian countries for several years as an alternative to PPI therapy.[20] The short-term safety and efficacy of vonoprazan is described in more detail in the New Drug Evaluation and in **Table 9**.

Most PPIs are metabolized primarily by cytochrome P450 2C19 (CYP2C19) into inactive metabolites.[21] The CYP2C19 genotype has been linked to PPI plasma concentration, efficacy, and adverse effects.[21] Approximately 5% of White people and 20% to 30% of people of South and East Asian descent are homozygous for a CYP2C19 mutation, which results in low CYP2C19 activity (i.e., slow metabolizers).[22] In 2021, the Clinical Pharmacogenetics Implementation Consortium (CPIC) published recommendations to facilitate interpretation of CYP2C19 genotyping to guide PPI prescribing.[21] First-generation PPIs include omeprazole, lansoprazole and pantoprazole. Second-generation PPIs include esomeprazole, rabeprazole, and dexlansoprazole. First-generation PPI plasma concentrations are more dependent on the CYP2C19 genotype.[21] The second generation PPIs esomeprazole and rabeprazole are less dependent on the genetic variability of CYP2C19.[21] Dexlansoprazole (R-lansoprazole) appears to share a similar metabolic pathway to lansoprazole.[21]

Upper endoscopy is the most widely used objective test for evaluating changes to the esophageal mucosa.[16] For patients with GERD symptoms who also have severe symptoms such as dysphagia, weight loss, bleeding, vomiting, or anemia, endoscopy should be performed as soon as feasible to rule out adenocarcinoma or Barrett's esophagus.[3] Severity of erosive esophagitis is classified based on the Los Angeles (LA) Classification Grading System (Grades A through D), described

in **Table 1**.[16] The criteria used by the LA classification describe the size and number of visible mucosal breaks, with or without overlying exudate.[16] The LA classification of erosive esophagitis is a validated scoring system and is frequently used in clinical practice.[16] Grade A and B esophagitis on the LA classification can be diagnostic of mild GERD in the presence of GERD symptoms, while LA grade C and D are usually diagnostic of severe GERD.[16] In patients with Grade C and D esophagitis, endoscopy is recommended after 8 weeks of PPI treatment to ensure healing and to evaluate for Barrett's esophagus, which can be difficult to detect when severe erosive esophagitis is present.[3]

Table 1. The Los Angeles Classification for Endoscopic Assessment of Erosive Esophagitis[16]

Rating	Description
Grade A	At least one mucosal break no longer than 5 mm, that does not extend between the tops of 2 mucosal folds
Grade B	At least one mucosal break more than 5 mm long, that does not extend between the tops of 2 mucosal folds
Grade C	At least one mucosal break that is continuous between the tops of the 2 or more mucosal folds, but involves less than 75% of the esophageal circumference
Grade D	At least one mucosal break which involves at least 75% of the esophageal circumference
Abbreviations: mm = millimeters	

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Pharmacological Treatment of GERD in Infants and Children:
An updated 2023 Cochrane review assessed the effects of pharmacological treatments (PPIs, H2RAs, prokinetics, and alginates) for management of GERD in infants and children.[1] This is an updated version of a 2014 Cochrane review.[1] Literature was searched through September 2022 for RCTs in children up to 16 years of age.[1] Thirty-six RCTs (n=2,251) met inclusion criteria.[1] Twelve new RCTs were included in the 2023 update.[1] Nineteen studies assessed infants only, 6 studies assessed infants and children, and 11 assessed children aged one year or older.[1]

The primary outcome was improvement in clinical symptoms, which was usually assessed through questionnaires completed by parents and childcare providers. The symptoms monitored in infants included: number of vomiting episodes, episodes of back arching, number of regurgitation episodes, failure to thrive, feeding difficulties and abdominal pain in infants.[1] In older children, the number of episodes of heartburn, epigastric pain, or regurgitation were assessed

through questionnaires completed by participants, parents, and health professionals.[1] Data is presented in 2 groups separated by age: infants up to 12 months old, and children aged 12 months to 16 years.[1]

Infants

Two studies assessed PPIs versus placebo and one study compared omeprazole with ranitidine.[1] No studies assessed prokinetics or magnesium alginate.[1] One small RCT compared omeprazole with placebo in 30 infants aged 3 to 12 months over 2 weeks.[1] In this trial, the mean difference between omeprazole and placebo in cry/fuss time in infants was 10 minutes/day (95% CI -89.1 to 69.1; very low-certainty of evidence).[1] The reflux index changed in the omeprazole group from 9.9 +/- 5.8% in 24 hours to 1.0 +/- 1.3% and in the placebo group from 7.2 +/- 6.0% to 5.3 +/- 4.9% in 24 hours (mean difference [MD] 7% lower, 95% CI -9.3 to -4.7; very low-certainty of evidence).[1] Reflux monitoring measures the degree of acidity in the esophagus during a 24-hour period by placing a catheter in the esophagus. This measures changes in the reflux index, but there is uncertainty about the value of this test due to lack of standardization and interpretation of the results.[23] In another placebo-controlled RCT of 52 neonates, esomeprazole did not reduce the number of GERD symptoms (observed from video and cardiorespiratory monitoring) compared to placebo over 2 weeks (MD 3.2 less episodes; 95% CI, -4.6 to -1.8; very low-certainty evidence).[1] There was no clear effect from omeprazole or esomeprazole on reducing GERD symptoms. Evidence for the efficacy of omeprazole and esomeprazole in 6resolving GERD symptoms in infants is uncertain.[1]

Symptomatic improvement of GERD symptoms was evaluated in a RCT that compared omeprazole versus ranitidine in 76 infants.[1] Omeprazole and ranitidine resulted in similar symptomatic improvement based on a weekly gastroesophageal reflux score over 2 weeks (very low-certainty evidence).[1] In the scoring tool used for this RCT, parents recorded the severity of 6 symptoms of GERD (back arching, choking/gagging, episodes of hiccups, irritability, refusal to feed, and vomiting/regurgitation).[24] The severity score ranged from 1 (not all severe) to 7 (most severe) for a total score of 42 points per day or 294 points per week.[24] Symptom scores in the omeprazole group changed from 51.9 +/- 5.4 to 2.4 +/- 1.2, and in the ranitidine group from 47 +/- 5.6 to 2.5 +/- 0.6 after two weeks: MD -4.97 (95% CI -7.33 to -2.61; very low-certainty evidence).[1]

Children

Two studies compared different doses of a PPI in children and found that PPIs at different doses may provide little to no symptomatic and endoscopic benefit in children.[1] Pantoprazole was evaluated at 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg in children aged 1 to 5 years (n=60).[1] By week 8, no difference was observed between 0.3 mg/kg and 1.2 mg/kg dosing (MD, 0.7; 95% CI, -0.4 to 1.8; very low-certainty evidence).[1] In another RCT (n=127), rabeprazole given at different doses (0.5 mg/kg and 1 mg/kg) provided similar symptom improvement.[1] Children over 1 year of age were divided into 2 groups based on weight (< 15 kg and ≥ 15 kg).[1] For the higher-weight group, symptom score mean difference between the two different dosing regimens was 2.3 (95% CI, -2.0 to 6.6; very low-certainty evidence), and for the lower-weight group, the total GERD symptom and severity score MD was 4.6 (95% CI, -2.9 to 12; very low-certainty evidence).[1] There were insufficient data to assess efficacy of other medications in children.[1]

In summary, there is very low-certainty evidence about symptom improvements for infants when treated with PPIs or H2RAs for GERD.[1] In children aged 1 year and older with GERD, there is very low-certainty evidence that rabeprazole and pantoprazole may or may not improve GERD outcomes.[1] No robust data exist for other medications.[1] Further studies in pediatric patients with longer follow-up are needed.[1]

Pharmacological Interventions for the Treatment of GERD In Adults and Children with Asthma

Acid reflux has been postulated as a trigger for asthma but published evidence is conflicting.[2] A 2021 Cochrane review updated a 2003 publication to assess the effectiveness of GERD treatment at improving asthma in adults and children.[2] Literature was searched through June 2020 and 23 studies (n=2,872) met inclusion

criteria.[2] Included studies reported data from 25 different countries.[2] Patients were mostly adults with moderate or severe asthma and GERD.[2] Pharmacological interventions included antacids, PPIs, H2RAs, and prokinetics (e.g. baclofen, domperidone, bethanechol).[2] Primary outcomes of interest were acute asthma exacerbations, hospital admissions, and emergency room visits.[2] Secondary outcomes included lung function as measured by spirometry, use of rescue medications, and asthma symptom scoring.[2] Twelve studies focused on PPIs and 5 studies evaluated H2RAs.[2] Most of the studies were judged to have moderate to high risk of bias due inadequate blinding of outcome assessment, incomplete outcome data, and selective reporting.[2]

Two studies reported on the number of participants who experienced a severe asthma exacerbation and could be pooled into a meta-analysis.[2] No difference between medical treatment with a PPI compared to placebo was found in terms of numbers of participants experiencing a moderate/severe exacerbation (odds ratio [OR] 0.53, 95% CI 0.17 to 1.63; n=1168; P=0.27; low-certainty evidence).[2] Medical treatment for GERD probably improved FEV_1 by a small amount (MD, 0.10 L; 95% CI, 0.05 to 0.15; moderate-certainty evidence) as well as use of rescue medications (MD, -0.71 puffs per day; 95% CI, -1.20 to -0.22; moderate-certainty evidence).[2] However, these mean improvements did not reach clinical importance.[2] There was not enough evidence to evaluate the effectiveness of GERD treatment in children, as only 2 studies included pediatric patients.[2]

After further review, 8 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses),[25-28] wrong study design of included trials (e.g., observational, review),[29-31] comparator (e.g., no control or placebo-controlled),[32,33] or outcome studied (e.g., non-clinical).

New Clinical Guidelines:

American College of Gastroenterology Clinical Guideline for the Management of Gastroesophageal Reflux Disease

The ACG updated guidance for management of GERD in 2022.[3] Strength of recommendations and quality of evidence regarding the use of PPIs and H2RAs for management of GERD and erosive esophagitis are summarized below.

- For patients with classic GERD symptoms of heartburn and regurgitation who have no alarming symptoms, start an 8-week trial of empiric PPIs once daily before a meal (strong recommendation; moderate-quality evidence).[3]
- Attempt to discontinue the PPIs in patients whose classic GERD symptoms respond to an 8-week empiric trial of PPIs (conditional recommendation; low-quality evidence).[3]
- Treat with PPIs instead of H2RAs for healing erosive esophagitis (strong recommendation; high-quality evidence).[3]
- Treat with PPIs instead of H2RAs for maintenance of erosive esophagitis (strong recommendation; moderate-quality evidence).[3]
- PPI administration should be 30 to 60 minutes before a meal rather than at bedtime for GERD symptom control (strong recommendation; moderate-quality evidence).[3]
- For patients with GERD who do not have erosive esophagitis or Barrett's esophagus, and whose symptoms have resolved with PPI therapy, an attempt should be made to discontinue PPIs (conditional recommendation; low-quality evidence).[3]
- For patients with GERD who require maintenance therapy with PPIs, the PPIs should be administered in the lowest dose that effectively controls GERD symptoms and maintains healing of reflux esophagitis (conditional recommendation; low-quality evidence).[3]
- Maintain PPI therapy indefinitely or refer for antireflux surgery for patients with LA grade C or D esophagitis (strong recommendation; moderate-quality evidence).[3]
- For patients with both extraesophageal symptoms (i.e. hoarseness, chronic cough, or laryngitis) and typical GERD symptoms (i.e. heartburn regurgitation), consider twice-daily PPI for 8 to 12 weeks before additional testing (conditional recommendation; low quality evidence).[3]

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- For patients with refractory GERD, PPI therapy should be optimized as the first step in therapeutic management (strong recommendation; moderate-quality evidence).[3] Optimization of PPI therapy includes verifying compliance, confirming that the PPI is taken 30–60 minutes before the first meal of the day for daily dosing and before the first and dinner meal for twice-daily dosing.[3]

Regarding the safety of long-term PPI treatment for GERD, the ACG suggests patients should be advised as follows: "*PPIs are the most effective medical treatment for GERD. Some medical studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. Those studies have flaws, are not considered definitive, and do not establish a cause-and-effect relationship between PPIs and the adverse conditions. High-quality studies have found that PPIs do not significantly increase the risk of any of these conditions except intestinal infections. Nevertheless, ACG cannot exclude the possibility that PPIs might confer a small increase in the risk of developing these adverse conditions. For the treatment of GERD, gastroenterologists generally agree that the well-established benefits of PPIs far outweigh their theoretical risks.*"[3]
In addition, the following suggestions regarding safety risks are included in the 2022 guidance:

- For patients with GERD on PPIs who have no other risk factors for bone disease, increased intake of calcium or vitamin D and routine bone mineral density testing are not recommended.[3]
- For patients with GERD on PPIs who have no other risk factors for vitamin B12 deficiency, increased intake of vitamin B12 and routine monitoring of serum B12 levels are not recommended.[3]
- For patients with GERD on PPIs who have no other risk factors for kidney disease, routine monitoring of serum creatinine levels are not recommended.[3]
- For patients with GERD on clopidogrel who have LA grade C or D esophagitis or whose GERD symptoms are not adequately controlled with alternative medical therapies, the highest quality data available suggest that the established benefits of PPI treatment outweigh cardiovascular risks.[3]
- PPIs can be used to treat GERD in patients with renal insufficiency with close monitoring of renal function or consultation with a nephrologist.[3]

New FDA Safety Alerts:
Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Labeling Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Dexlansoprazole Lansoprazole[4]	Dexilant Prevacid	9/2020	Warnings and Precautions	Dexlansoprazole is not recommended in pediatric patients less than two years of age because of risk of heart valve thickening. Nonclinical studies in juvenile rats with lansoprazole have demonstrated an adverse effect of heart valve thickening. Dexlansoprazole is the R-enantiomer of lansoprazole.
All PPIs[5]		11/2020	Warnings and Precautions	Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash, or arthralgia). Discontinue PPI and evaluate patients with suspected acute TIN.

All PPIs[5]		3/2022	Warnings and Precautions	Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs. Discontinue PPIs at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.
All PPIs[5]		3/2022	Warnings and Precautions	Serious adverse events with PPIs from hypomagnesemia include tetany, arrhythmias, and seizures. Hypomagnesemia from PPIs may lead to hypocalcemia or hypokalemia and may exacerbate underlying hypocalcemia in at-risk patients. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. Consider monitoring magnesium and calcium levels prior to initiation of PPIs and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium or calcium as necessary. If hypocalcemia is refractory to treatment, consider discontinuing the PPI.

Randomized Controlled Trials:
A total of 112 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:
See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The PCAB vonoprazan was approved by the FDA in November 2023 for healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.[6] The recommended dose for erosive esophagitis healing is 20 mg orally once a day for 8 weeks.[6] To maintain healing of erosive esophagitis, the recommended dose is 10 mg orally once a day for up to 6 months.[9] Vonoprazan is also FDA-approved in combination with amoxicillin alone or with amoxicillin and clarithromycin to treat *H. pylori* infection.[3] This indication is reviewed in a separate class update.
Vonoprazan prevents gastric acid secretion by inhibiting the hydrogen-potassium-ATPase pump in a potassium-competitive manner.[6] Initial clinical studies of vonoprazan were primarily conducted in Japan. Three double-blind RCTs in Japanese patients showed vonoprazan 20 mg daily was noninferior to lansoprazole 30 mg daily in proportion of patients with endoscopically confirmed erosive esophagitis healing at 8 weeks.[34-36] These studies included patients with *H. pylori*. Studies have shown that PPIs have greater efficacy in people with *H. pylori* infection compared do those who are not infected.[7] Some studies have also shown that poor metabolizers of CYP2C19 are more common in Asian populations compared to Western populations.[37] The inhibition of CYP2C19 can lead to greater

acid inhibition with PPIs, but not PCABs.[7] Because Asian and Western populations differ in factors that may influence acid inhibition, assessment of vonoprazan efficacy in Western subjects was evaluated in a randomized trial (NCT04124926), which is described and evaluated below and in **Table 6**.[7]

The phase 3, active-controlled, double-blind RCT conducted in the U.S. and Europe enrolled 1024 adult patients with endoscopically confirmed erosive esophagitis.[7] Endoscopic photographs were read by blinded, centrally located specialists prior to patient enrollment.[7] Patients who were positive for *H. pylo*ri infection or who had Barrett's esophagus or definite dysplastic changes in the esophagus at baseline were excluded from the study.[7] Severity of erosive esophagitis was based on the LA Classification Grading System (see **Table 1**).[7] Sixty-six percent of patients had mild erosive esophagitis (Grades A or B) and 34% of patients had severe erosive esophagitis (Grades C or D) prior to randomization.[6] About 30% of enrolled patients had used a PPI prior to randomization.[7] Patients in the trial had a mean age of 51 years (range 18 to 84 years); 53% were female; 12% identified as Hispanic; 91% identified as White, 6% as Black or African American, and 3% identified as another racial group.[6]

During the initial 8-week healing phase, patients were randomized 1:1 to receive vonoprazan 20 mg once a day or lansoprazole 30 mg once a day.[7] The primary endpoint was percentage of patients with endoscopically confirmed healing of all grades of erosive esophagitis by week 8 in a noninferiority comparison (noninferiority margin, 10%, lower bound of 95% CI > -10%).[7] Non-inferiority comparisons were chosen for the primary analyses of efficacy endpoints in this trial, with subsequent superiority analyses pre-specified if non-inferiority was established.[7] All endoscopies during the RCT were centrally read and adjudicated by specialists blinded to patient data.[7] A secondary endpoint was a noninferiority assessment based on relief of heartburn symptoms over 24 hours during the 8 week phase of the RCT (noninferiority margin, 15%, lower bound of 95% CI > -15%).[7] Patients recorded severity of daytime and nighttime heartburn on a 5-point ordinal scale (0=none to 5=very severe) in an electronic diary.[7] Treatment effect was also assessed based on LA classification of mild erosive esophagitis (grades A/B) and severe erosive esophagitis (grades C/D) at week 2.[7]

The primary analysis population was the mITT data set, defined as all subjects randomized who had documented erosive esophagitis at baseline in the healing phase or documented healing of erosive esophagitis at baseline in the maintenance phase and received at least 1 dose of the study medication.[7] The per-protocol (PP) population criteria included subjects who received their assigned study medication, were compliant with treatment, and had an endoscopy performed by week 8 in the healing phase and by week 24 in the maintenance phase.[7] Among 1024 subjects in the 8-week healing phase, vonoprazan was noninferior to lansoprazole in the primary analysis of healing in the mITT population (92.9% vs. 84.6%; difference, 8.3%; 95% CI, 4.5 to 12.2).[7] Results using the PP set were consistent with the mITT population, which showed vonoprazan was noninferior to lansoprazole for healing of erosive esophagitis (94.7% vs. 86.6%; difference, 8.1%; 95% CI 4.1 to 11.9).[7] Secondary analyses showed vonoprazan was noninferior in heartburn-free days at 8 weeks (34.6% vs. 35.5%; difference, 2.7%; 95% CI, −1.6 to 7.0).[7] A greater treatment effect was observed with vonoprazan 20 mg versus lansoprazole 30 mg for healing of erosive esophagitis at week 2 in subjects with grade C or D erosive esophagitis at baseline (70.2% vs. 52.6%; difference; 17.6%; 95% CI 7.5 to 27.4; p=0.0008 for superiority based on predefined sequential analysis of secondary endpoint).[7] A similar result for this endpoint was observed at week 8, but hypothesis testing was not performed because the prior endpoint (sustained heartburn resolution) did not show superiority in the fixed-sequence analysis.[7]

Subjects (n=878) who showed endoscopically confirmed healed erosive esophagitis at Week 8 were re-randomized 1:1:1 into a 24-week maintenance phase to receive either vonoprazan 10 mg once daily, vonoprazan 20 mg once daily, or lansoprazole 15 mg once daily.[7] Maintenance of esophagitis healing and resolution of heartburn symptoms were evaluated over 24 weeks, and assessed in a noninferiority comparison.[7] Vonoprazan was noninferior to lansoprazole at Week 24 in the analysis of erosive esophagitis healing in the mITT population (vonoprazan 20 mg vs. lansoprazole 15 mg: difference, 8.7%; 95% CI, 1.8 to 15.5 and vonoprazan 10 mg vs. lansoprazole 15 mg: difference, 7.2%; 95% CI, 0.2 to 14.1).[7] The noninferiority of vonoprazan 20 mg and vonoprazan 10 mg versus lansoprazole 15 mg was demonstrated for the percentage of 24-hour heartburn-free days (vonoprazan 20 mg vs. lansoprazole 15 mg: 80.6% vs. 78.6%; 95% CI, -

2.6 to 6.7; vonoprazan 10 mg vs. lansoprazole 15 mg: 80.9% vs 78.6%; 95% CI, -2.3 to 6.8), with lower confidence bounds of -2.6% and -2.3%, respectively, and the mean treatment difference higher than the non-inferiority bound of -15%.[7] Results using the PP set were consistent with the mITT set.[7] In the preplanned superiority analysis of secondary endpoints, vonoprazan 20 and 10 mg had higher rates of erosive esophagitis healing at Week 24 that were statistically significant compared to lansoprazole 15 mg (90.7% and 89.2% vs. 79.7%, respectively, P<0.0001 for both comparisons).[7] Among subjects with Grade C or D erosive esophagitis at baseline, vonoprazan 20 mg and vonoprazan 10 mg were superior to lansoprazole 15 mg for the maintenance of erosive esophagitis healing at Week 24, another secondary endpoint (77.2% vs 61.5%, P=0.020 and 74.7% vs 61.5%, P=0.049, respectively).[7]

Study limitations are related to generalizability of results, lack of long-term safety data, and the noninferiority study design. The study population was primarily comprised of subjects who identified as White, which limits the generalizability of the results to other racial groups.[7] The study is also not generalizable to patients with *H. pylori* infection.[7] Given that PPIs may have greater efficacy in individuals with *H. pylori* infection, smaller differences may have occurred with inclusion of subjects positive for *H. pylori* infection.[7] In addition, the results cannot be generalized to all patients presenting with GERD-like symptoms.[7] Patients with symptoms such as heartburn but without erosive esophagitis represent a more heterogeneous group with less consistent response to gastric acid inhibition.[7] Recurrence rates of erosive esophagitis after 8 to 24 weeks of vonoprazan treatment are not known.[7] The long-term effect of vonoprazan on risks of bone fracture, kidney impairment, and *Clostridioides difficile*-associated diarrhea is unknown based on the results of this trial. Finally, the primary analysis of this study was a noninferiority assessment, so it is not clear if there are differences in efficacy between vonoprazan and lansoprazole over 8 weeks for healing of erosive esophagitis and over 24 weeks to maintain healing. A superiority analysis was only conducted for secondary endpoints, based on fixed sequence analysis. A superiority study design would have provided more robust data about the comparative effectiveness of vonoprazan with lansoprazole for the primary endpoints of healing and maintenance of erosive esophagitis healing.

A few studies assessed the effectiveness of vonoprazan in patients with nonerosive reflux disease (NERD). Non-erosive reflux disease is characterized by episodic heartburn symptoms related to acid reflux without endoscopically detectable damage to the esophageal mucosa.[38] Vonoprazan has not yet received FDA approval for this indication, although the manufacturer has submitted a request for the FDA to review the evidence for the use of vonoprazan in patients with NERD. In a Japanese double blind, placebo-controlled phase 3 RCT, adults with NERD and recurrent acid reflux symptoms received vonoprazan 10 mg, vonoprazan 20 mg, or placebo.[39] The primary efficacy outcome was the proportion of days without heartburn symptoms measured by patient scores over 4 weeks.[39] The median proportion of days without heartburn was 7.4% for placebo, 10.3% for vonoprazan 10 mg, and 12.0% for vonoprazan 20 mg.[39] The proportion of days without heartburn was not statistically significant between the vonoprazan and placebo groups (p=0.2310 [10 mg] and p=0.0504 [20 mg]).[39] The mean severity of heartburn was significantly higher with placebo (median score = 1.07) than with vonoprazan 10 mg (median score = 0.99; P=0.04) and 20 mg (median score = 0.96; P=0.014).[39] In another phase 3 RCT that included Japanese adults with NERD and recurrent heartburn, vonoprazan 10 mg daily given for 4 weeks was similar to placebo with respect to the proportion of days without heartburn (72.55% vs. 61.50%; P=0.064).[40] However, improvement in heartburn symptoms by week 2 was associated with a greater proportion of days without heartburn during the treatment period in the vonoprazan group compared with the placebo group (P<0.05).[40] A study conducted at 54 sites in the U.S. evaluated the time to response and the duration of response to several doses of on-demand vonoprazan in adults with NERD who had achieved complete symptom resolution during a 4 week course of daily vonoprazan 20 mg treatment.[38] After the 4-week open-label period, eligible patients (n=207) were randomized to vonoprazan 10, 20, 40 mg or placebo in a 6-week on-demand dosing period.[38] During the on-demand period, study drug was only taken in response to the onset of a heartburn episode, with only one dose allowed per 24-hour period.[38] Evaluable heartburn episodes were relieved within 3 hours with no further symptoms for the next 24 hours in 56.0% of the 10 mg group; 60.6% in the 20 mg group; and 70.0% in the 40 mg group, compared with 27.3% in the placebo group (p<0.0001 versus placebo for each vonoprazan group).[38] No serious treatment-emergent adverse events were reported.[38]

Clinical Safety:
Adverse reactions reported in at least 2% of patients in the vonoprazan arm in the phase 3 RCT are presented in **Table 4** (8-week healing phase) and **Table 5** (24-week maintenance phase).[6] No *Clostridioides difficile* (*C. difficile*) infections were reported in the 32-week RCT.[7] However, it is possible *C. difficile* infections may occur with vonoprazan treatment so the manufacturer recommends using shortest treatment duration as appropriate to reduce risk of *C. difficile* infection.[6]

Table 3. Adverse Reactions Reported in at Least 2% of Adult Patients with Erosive Esophagitis (8-Week Healing Phase)[6]

Adverse Reactions	Vonoprazan 20 mg once daily (n=514)	Lansoprazole 30 mg once daily (n=510)
Gastritis	3%	2%
Diarrhea	2%	3%
Abdominal Distension	2%	1%
Abdominal Pain	2%	1%
Nausea	2%	1%

Table 4. Adverse Reactions Reported in at Least 3% of Adult Patients with Erosive Esophagitis (24-Week Maintenance Phase)[6]

Adverse Reactions	Vonoprazan 10 mg once daily (n=296)	Lansoprazole 15 mg once daily (n=297)
Gastritis	6%	3%
Abdominal Pain	4%	2%
Dyspepsia	4%	3%
Hypertension	3%	2%
Urinary Tract Infection	3%	2%

In people with an estimated glomerular filtration (eGFR) less than 30 mL/min or moderate to severe hepatic impairment (Child-Pugh Class B or C), vonoprazan dosing for treatment of erosive esophagitis should be reduced to 10 mg once daily.[6] Vonoprazan is not recommended to treat *H. pylori* in people with an eGFR less than 30 mL/min or Child-Pugh class B or C.[6] No vonoprazan dosage adjustments are recommended for people with an eGFR rate greater than 30 mL/minute or mild hepatic impairment (Child-Pugh Class A).[6] There are no adequate and well-controlled studies of vonoprazan in pregnant or lactating women or pediatric patients.[6]

Due to extensive hepatic metabolism, there are numerous drug interactions to consider with vonoprazan. Vonoprazan reduces gastric acidity which may affect the absorption of drugs dependent on an acidic environment for absorption.[6] Vonoprazan is an inhibitor of CYP3A4 and CYP2C19 enzymes and may increase the serum

DRAFT

concentration of drugs metabolized by these routes or inhibit conversion of drugs to an active metabolite.[6] Finally, strong or moderate CYP3A inducers may reduce the effectiveness of vonoprazan and coadministration should be avoided.

Vonoprazan may also interact with laboratory testing.[6] The chromogranin A (CgA) measurement may result in false-positive diagnostic evaluations for neuroendocrine tumors due to CgA levels increasing with decreases in gastric acidity.[41] The secretin stimulation test may result in false suggestion of gastrinomas due to hyper-response in gastrin secretion.[41] If either of these diagnostic tests are needed, vonoprazan should be stopped 14 days prior to testing.[6]

Look-alike / Sound-alike Error Risk Potential: International Issues – Vonoprazan may be confused with revaprazan and the brand name for vonoprazan in Japan, Malaysia and Singapore may be confused with bosentan.[42]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Endoscopically confirmed healing of erosive esophagitis
2) Decrease in the number of days with heartburn symptoms
3) Development of esophageal cancer
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Endoscopically confirmed healing of erosive esophagitis

Table 5. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	Inhibits the hydrogen-potassium-ATPase enzyme system in gastric parietal cells which blocks the final step of acid production
Oral Bioavailability	Time to peak absorption: 1 to 3 hours
Distribution and Protein Binding	Volume of distribution: 782 to 1,270 L (dose dependent: 20 mg twice daily vs. 10 mg once daily) Protein binding ranges from 85 to 88%
Elimination	67% of dose recovered in urine and 31% of dose recovered in feces (as unchanged drug)
Half-Life	6.8 to 7.9 hours depending on daily dose (20 mg twice daily vs. 20 mg once a day)
Metabolism	Metabolized to inactive metabolites via multiple pathways including CYP3A4/5, CYP2B6, CYP2C9, CYP2C19, and CYP2D6

Abbreviations: mg = milligram; L = Liter

DRAFT

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Laine et al.[7] DB, AC, NI, MC, phase 3 RCT 2 phases: 8-week healing phase and 24-week maintenance phase	**8-week healing phase:** 1. Vonoprazan 20 mg PO daily Vs. 2. Lansoprazole 30 mg PO daily **24-week maintenance phase:** 1. Vonoprazan 10 mg PO daily Vs. 2. Vonoprazan 20 mg PO daily Vs. 3. Lansoprazole 15 mg PO daily	Demographics: -Mean age: 51 yo -Female Gender: 53% -Ethnicity Hispanic: 12% -Race White: 91% Black: 6% Other: 3% -Current Smoker: 14% -PPI use: 30% -Baseline EE Severity using LA Classification Grade A: 35% Grade B: 30% Grade C: 30% Grade D: 3% Key Inclusion Criteria: -Age ≥18 y -endoscopic diagnosis of EE LA grades A,B, C and D Key Exclusion Criteria: -Positive *H. pylori* or recent *H. pylori* infection -Barrett's esophagus -Active gastric or duodenal ulcer or gastrointestinal bleeding in past 4 weeks -Zollinger-Ellison syndrome	**8-week phase** ITT: 1. 514 2. 510 PP: 1. 483 2. 481 Attrition: 1. 31 (6%) 2. 29 (6%) **24-week phase** ITT: 1. 296 2. 296 3. 297 PP: 1. 274 2. 269 3. 269 Attrition: 1. 24 (8%) 2. 27 (9%) 3. 28 (9%)	**8-week phase** Primary Endpoint: % of patients with endoscopic EE healing by week 8 (NI assessment) in the mITT population. 1. 478 (92.9%) 2. 431 (84.6%) Difference: 8.3% 95% CI 4.5 to 12.2 P<0.0001 for NI Secondary Endpoints: % of patients with 24-hour heartburn-free days over 8 weeks (NI assessment) 1. 343 (66.8%) 2. 327 (64.1%) Difference: 2.7% 95% CI -1.6 to 7.0 Healing of EE in subgroups with LA grade C or D at week 2 1. 70.2% 2. 52.6% Difference: 17.6% 95% CI 7.4 to 27.4 P=0.0008 for superiority **24-week phase:** Primary Endpoint: % of patients with endoscopic EE healing by week 24 (NI assessment). 1. 234 (79.2%) 2. 239 (80.7%) 3. 214 (72%) 1 vs. 3 Difference: 7.2%	N/A N/A N/A	**8-week phase** AEs 1. 155 (30%) 2. 149 (29%) SAEs 1. 3 (0.6%) 2. 3 (0.6%) AEs leading to treatment discontinuation 1. 5 (1%) 2. 11(2%) Bone Fracture 1. 1 (0.2%) 2. 1 (0.2%) ALT or AST > 3 x ULN 1. 2 (0.4%) 2. 1 (0.2%) **24-week phase** AEs 1. 167 (54%) 2. 160 (54%) 3. 150 (51%) SAEs 1. 10 (3.4%) 2. 14 (4.7%) 3. 7 (2.4%) AEs leading to treatment discontinuation 1. 8 (3%) 2. 2 (0.7%) 3. 2 (0.7%) Bone Fracture	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Central randomization sequence generated using IRT. Groups were stratified by baseline LA classification grade of EE (A/B and C/D). Baseline characteristics were similar between groups. Performance Bias: Low. Study medications had identical appearance and were administered 30 minutes before morning meal. Quadruple blinding: patients, providers, investigators, outcomes assessors. Detection Bias: Low. All endoscopic readings were performed at a central site by physicians blinded to patient data. Attrition Bias: Low. Patients with missing endoscopy results were imputed as non-responders. Reporting Bias: Low. Protocol is available online. All prespecified endpoints were reported as planned. Other Bias: High. Manufacturer participated in study design and analysis. Study funded by manufacturer. Several authors report conflicts of interest as consultants for the manufacturer. **Applicability**: Patient: Enrolled patients were primarily White with EE which limits generalizability to other populations or patients with *H. Pylori*. Intervention: Vonoprazan doses determined from 3 Japanese RCTs in patients with EE. Comparator: Lansoprazole 30 mg once a day is an appropriate active comparator drug and dose for people with EE. Outcomes: Percent of patients with endoscopically-confirmed EE healing is an appropriate outcome to assess efficacy. Setting: 77 sites in the US and 34 sites in Europe (Poland, Czech Republic, Hungary, Bulgaria, and United Kingdom).

DRAFT

				95% CI 0.2 to 14.01 P<0.0001 for NI 2 vs. 3 Difference: 8.7% 95% CI 1.8 to 15.5 P<0.0001 for NI <u>Secondary Endpoint:</u> Percentage of patients with 24-hour heartburn-free days over 24 weeks (NI assessment) 1. 240 (80.9%) 2. 239 (80.6%) 3. 233 (78.6%) 1 vs. 3 Difference: 2.3% 95% CI -2.3 to 6.8 2 vs. 3 Difference: 2.0% 95% CI -2.6 to 6.7 Maintenance of EE healing in LA grade C/D 1. 74.7% 3. 61.5% P=0.0490	N/A NA NA NA NA	1. 4 (1.4%) 2. 2 (0.7%) 3. 1 (0.3%) <u>ALT or AST > 3 x ULN</u> 1. 1 (0.3%) 2. 3 (1%) 3. 6 (2%) 95% CI and p-values NR		

<u>Abbreviations</u>: AC = active comparator; AEs = adverse events; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = aspartate aminotransferase; CI = confidence interval; DB = double blind; EE = erosive esophagitis; IRT = interactive response technology; ITT = intention to treat; LA = Los Angeles; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = noninferiority; NNH = number needed to harm; NNT = number needed to treat; NR =not reported; PO = by mouth; PP = per protocol; RCT = randomized controlled trial; SAEs = serious adverse events; ULN = upper limit of normal; y = years

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DRAFT

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DRAFT

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Appendix 1: Current Preferred Drug List

Histamine-2 Receptor Antagonists

Generic	Brand	Route	Form	PDL
ranitidine HCl	ZANTAC	ORAL	SYRUP	Y
famotidine/Ca carb/mag hydrox	ACID REDUCER COMPLETE	ORAL	TAB CHEW	Y
famotidine/Ca carb/mag hydrox	ACID REDUCER-ANTACID	ORAL	TAB CHEW	Y
famotidine/Ca carb/mag hydrox	DUAL ACTION COMPLETE	ORAL	TAB CHEW	Y
famotidine	ACID REDUCER	ORAL	TABLET	Y
famotidine	FAMOTIDINE	ORAL	TABLET	Y
famotidine	FAMOTIDINE	ORAL	TABLET	Y
famotidine	HEARTBURN RELIEF	ORAL	TABLET	Y
famotidine	PEPCID	ORAL	TABLET	Y
ranitidine HCl	RANITIDINE HCL	ORAL	TABLET	Y
ranitidine HCl	ZANTAC	ORAL	TABLET	Y
nizatidine	NIZATIDINE	ORAL	CAPSULE	N
cimetidine HCl	CIMETIDINE HCL	ORAL	SOLUTION	N
famotidine	FAMOTIDINE	ORAL	SUSP RECON	N
famotidine	PEPCID RPD	ORAL	TAB RAPDIS	N
cimetidine	CIMETIDINE	ORAL	TABLET	N
cimetidine	CIMETIDINE	ORAL	TABLET	N

Proton Pump Inhibitors

Generic	Brand	Route	Form	PDL
dexlansoprazole	DEXILANT	ORAL	CAP DR BP	Y
dexlansoprazole	DEXLANSOPRAZOLE DR	ORAL	CAP DR BP	Y
lansoprazole	ACID REDUCER	ORAL	CAPSULE DR	Y
lansoprazole	LANSOPRAZOLE	ORAL	CAPSULE DR	Y
lansoprazole	LANSOPRAZOLE	ORAL	CAPSULE DR	Y
omeprazole	OMEPRAZOLE	ORAL	CAPSULE DR	Y
lansoprazole	PREVACID	ORAL	CAPSULE DR	Y
lansoprazole	PREVACID 24HR	ORAL	CAPSULE DR	Y
rabeprazole sodium	ACIPHEX	ORAL	TABLET DR	Y
pantoprazole sodium	PANTOPRAZOLE SODIUM	ORAL	TABLET DR	Y
pantoprazole sodium	PROTONIX	ORAL	TABLET DR	Y
rabeprazole sodium	RABEPRAZOLE SODIUM	ORAL	TABLET DR	Y
omeprazole/sodium bicarbonate	OMEPRAZOLE-SODIUM BICARBONATE	ORAL	CAPSULE	N
omeprazole/sodium bicarbonate	OMEPRAZOLE-SODIUM BICARBONATE	ORAL	CAPSULE	N

DRAFT

omeprazole/sodium bicarbonate	ZEGERID	ORAL	CAPSULE	N
omeprazole magnesium	ACID REDUCER	ORAL	CAPSULE DR	N
esomeprazole magnesium	ESOMEPRAZOLE MAGNESIUM	ORAL	CAPSULE DR	N
esomeprazole magnesium	ESOMEPRAZOLE MAGNESIUM	ORAL	CAPSULE DR	N
esomeprazole magnesium	NEXIUM	ORAL	CAPSULE DR	N
omeprazole magnesium	OMEPRAZOLE MAGNESIUM	ORAL	CAPSULE DR	N
pantoprazole sodium	PANTOPRAZOLE SODIUM	ORAL	GRANPKT DR	N
pantoprazole sodium	PROTONIX	ORAL	GRANPKT DR	N
omeprazole/sodium bicarbonate	OMEPRAZOLE-SODIUM BICARBONATE	ORAL	PACKET	N
omeprazole/sodium bicarbonate	ZEGERID	ORAL	PACKET	N
omeprazole/sodium bicarbonate	KONVOMEP	ORAL	SUSP RECON	N
esomeprazole magnesium	ESOMEPRAZOLE MAGNESIUM	ORAL	SUSPDR PKT	N
esomeprazole magnesium	NEXIUM	ORAL	SUSPDR PKT	N
omeprazole magnesium	PRILOSEC	ORAL	SUSPDR PKT	N
lansoprazole	LANSOPRAZOLE	ORAL	TAB RAP DR	N
lansoprazole	LANSOPRAZOLE	ORAL	TAB RAP DR	N
omeprazole	OMEPRAZOLE	ORAL	TAB RAP DR	N
lansoprazole	PREVACID	ORAL	TAB RAP DR	N
esomeprazole magnesium	ESOMEPRAZOLE MAGNESIUM	ORAL	TABLET DR	N
omeprazole	OMEPRAZOLE	ORAL	TABLET DR	N
omeprazole magnesium	OMEPRAZOLE MAGNESIUM	ORAL	TABLET DR	N
omeprazole	OMEPRAZOLE	ORAL	TABLET DR	

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Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to March Week 5 2024; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to April 08, 2024

1	Esophagitis/ or Esophagitis, Peptic/	6138
2	Gastroesophageal Reflux/	21812
3	Proton Pump Inhibitors/	13499
4	Histamine H2 Antagonists/	4105
5	exp Omeprazole/	7949
6	exp Pantoprazole/	1402
7	exp Dexlansoprazole/	86
8	exp Esomeprazole/	1260
9	exp Lansoprazole/	2072
10	exp Rabeprazole/	1052
11	exp Famotidine/	964
12	exp Ranitidine/	2132
13	exp Cimetidine/	1679
14	nizantidine.mp.	0
15	vonoprazan.mp.	388
16	potassium-competitive acid blockers.mp. or Anti-Ulcer Agents/	10093
17	1 or 2	25868
18	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	27882
19	17 and 18	5219
20	limit 19 to (english language and humans and yr="2020 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	108
21	Zollinger-Ellison Syndrome/	522
22	Barrett Esophagus/	7982
23	21 or 22	8500
24	18 and 23	677
25	20 and 24	3

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Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VOQUEZNA® safely and effectively. See full prescribing information for VOQUEZNA.

VOQUEZNA (vonoprazan) tablets, for oral use
Initial U.S. Approval: 2022

----------INDICATIONS AND USAGE----------

VOQUEZNA is a potassium-competitive acid blocker indicated:

- for healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults. (1)
- to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults. (1)
- in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori (H. pylori)* infection in adults. (1)
- in combination with amoxicillin for the treatment of *H. pylori* infection in adults. (1)

---------- DOSAGE AND ADMINISTRATION ----------

Recommended Dosage:

- *Healing of Erosive Esophagitis:* 20 mg once daily for 8 weeks. (2.1)
- *Maintenance of Healed Erosive Esophagitis:* 10 mg once daily for up to 6 months. (2.1)
- *Treatment of H. pylori Infection:* see full prescribing information. (2.1)
- See also full prescribing information for the recommended dosage by indication for patients with renal or hepatic impairment. (2.2, 2.3)

Administration Instructions:

- Take with or without food. (2.4)
- Swallow whole; do not chew or crush. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 10 mg and 20 mg of vonoprazan. (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to vonoprazan or any component of VOQUEZNA. (4)
- Rilpivirine-containing products. (4, 7)

---------- WARNINGS AND PRECAUTIONS----------

- Gastric Malignancy: Symptomatic response to treatment does not preclude the presence of gastric malignancy; consider additional follow-up and diagnostic testing. (5.1)
- Acute Tubulointerstitial Nephritis: Discontinue treatment and evaluate patients. (5.2)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): May be associated with an increased risk; use the shortest duration of treatment appropriate to the condition. (5.3)
- Bone Fracture, including Osteoporosis-related Fracture: Use the shortest duration of treatment appropriate to the condition. (5.4)
- Severe Cutaneous Adverse Reactions: Discontinue at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation. (5.5)
- Vitamin B12 (Cobalamin) Deficiency: Long-term use may lead to malabsorption or deficiency; consider further workup if clinical symptoms are present. (5.6)
- Hypomagnesemia and Mineral Metabolism: Consider monitoring magnesium levels prior to starting treatment and periodically if prolonged treatment is expected, or if concomitant use of digoxin or other drugs that cause hypomagnesemia. (5.7)
- Interactions with Investigations for Neuroendocrine Tumors: Increased chromogranin A (CgA) levels may interfere with diagnostic investigations; temporarily stop VOQUEZNA at least 14 days before assessing CgA levels. (5.8, 7)
- Fundic Gland Polyps: Risk increases with long-term use; use the shortest duration of treatment appropriate to the condition. (5.9)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions in VOQUEZNA-treated patients are:

- Healing of Erosive Esophagitis (≥2%): gastritis, diarrhea, abdominal distension, abdominal pain, and nausea. (6.1)
- Maintenance of Healed Erosive Esophagitis (≥3%): gastritis, abdominal pain, dyspepsia, hypertension, and urinary tract infection. (6.1)
- Treatment of *H. pylori* Infection (≥2%): diarrhea, dysgeusia, vulvovaginal candidiasis, abdominal pain, headache, hypertension, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Phathom Pharmaceuticals, Inc. at toll-free phone 1-888-775-7428 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

See full prescribing information for a list of clinically important drug interactions. (7)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Breastfeeding not recommended during treatment. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2023

Appendix 4: Key Inclusion Criteria

Population	Patients with an indication for gastric acid suppression
Intervention	Proton pump inhibitor, histamine receptor antagonist therapy, and potassium-competitive acid blocker
Comparator	Placebo or active treatment regimen
Outcomes	Dyspepsia, ulcer healing rates, erosive esophagitis healing rates, quality of life
Timing	Symptom onset
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Proton Pump Inhibitors (PPIs)

Goals:

- Promote PDL options
- Restrict PPI use to patients with OHP-funded conditions
- Allow case-by-case review for members covered under the EPSDT program.

Requires PA:

- Preferred PPIs beyond 68 days' duration
- Non-preferred PPIs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/
- Individual components for treatment of *H. pylori* that are preferred products

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a preferred PPI?	**Yes:** Go to #6	**No:** Go to #3

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3. Is the treating diagnosis an OHP-funded condition (see **Table**)?	**Yes:** Go to #5	**No:** Current age ≥ 21 years: Pass to RPh; deny, not funded by OHP. Current age < 21 years: Go to #4
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
5. Will the prescriber consider changing to a preferred PPI product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives.	**No:** Go to #6
6. Has the patient already received 68 days of PPI therapy in past year for either of the following diagnoses: • Esophagitis or gastro-esophageal reflux disease with or without esophagitis (K20.0-K21.9); or • Current *H. pylori* infection?	**Yes:** Go to #9	**No:** Go to #7
7. Does the patient have recurrent, symptomatic erosive esophagitis that has resulted in previous emergency department visits or hospitalization?	**Yes:** Approve for 1 year	**No:** Go to #8
8. Does the patient have a history of gastrointestinal ulcer or bleed and have one or more of the following risk factors? a. Age 65 years or older b. Requires at least 3 months of continuous daily: i. Anticoagulant; ii. Aspirin (all doses) or non-selective NSAID; or iii. Oral corticosteroid	**Yes:** Approve for 1 year	**No:** Go to #9

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9. Are the indication, daily dose and duration of therapy consistent with criteria outlined in the **Table**? Message: OHP-funded conditions are listed in the **Table**.	**Yes:** Approve for recommended duration.	**No:** Pass to RPh. Deny; medical appropriateness Message: Patient may only receive 8 weeks of continuous PPI therapy. RPh may approve a quantity limit of 30 doses (not to exceed the GERD dose in the **Table**) over 90 days if time is needed to taper off PPI. Note: No specific PPI taper regimen has proven to be superior. H2RAs may be helpful during the taper. Preferred H2RAs are available without PA.

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Table. Dosing and Duration of PPI Therapy for OHP Funded Conditions.

Funded OHP Conditions*	Maximum Duration	Maximum Daily Dose
GERD: Esophageal reflux (K219) Esophagitis (K208-K210)	8 weeks* *Treatment beyond 8 weeks is not funded by OHP.	Dexlansoprazole 30 mg Dexlansoprazole Solu Tab 30 mg Esomeprazole 20 mg Lansoprazole 15 mg Omeprazole 20 mg Pantoprazole 40 mg Rabeprazole 20 mg
H. pylori Infection (B9681)	2 weeks	Dexlansoprazole 60 mg Dexlansoprazole 30 mg† Esomeprazole 40 mg Lansoprazole 60 mg Omeprazole 40 mg Pantoprazole 80 mg Rabeprazole 40 mg
Duodenal Ulcer (K260-K269)	4 weeks	
Gastric Ulcer (K250-K259)	8 weeks	
Peptic ulcer site unspecified (K270-K279)	12 weeks	
Achalasia and cardiospasm (K220) Barrett's esophagus (K22.70; K22.71x) Dyskinesia of esophagus (K224) Esophageal hemorrhage (K228) Eosinophilic Esophagitis (K200) Gastritis and duodenitis (K2900-K2901; K5281) Gastroesophageal laceration-hemorrhage syndrome (K226) Gastrojejunal ulcer (K280-K289) Malignant mast cell tumors (C962) Multiple endocrine neoplasia [MEN] type I (E3121) Neoplasm of uncertain behavior of other and unspecified endocrine glands (D440; D442; D449) Perforation of Esophagus (K223) Stricture & Stenosis of Esophagus (K222) Zollinger-Ellison (E164)	1 year	

*A current list of funded conditions is available at: https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Prioritized-List.aspx
† Dexlansoprazole SoluTab 30 mg (given as 2 SoluTabs at once) are not recommended for healing of erosive esophagitis.

P&T / DUR Review: *8/24 (DM); 10/22 (DM); 10/20 (KS), 5/17(KS); 1/16; 5/15; 3/15; 1/13; 2/12; 9/10; 3/10; 12/09; 5/09; 5/02; 2/02; 9/01, 9/98*
Implementation: *TBD; 1/1/23; 11/1/20; 6/8/16; 2/16; 10/15; 7/15; 4/15; 5/13; 5/12; 1/11; 4/10; 1/10; 9/06, 7/06, 10/04, 3/04*

Potassium-Competitive Acid Blockers

Goal(s):

- Promote use of potassium-competitive acid blockers (PCABs) in adults that is consistent with medical evidence.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 8 weeks for erosive esophagitis healing and up to 24 weeks for maintenance of erosive esophagitis healing.

Requires PA:

- Vonoprazan (VOQUENZA) oral tablets

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Recommended Vonoprazan Dosing Based on Degree of Hepatic Impairment and Indication

Classification	Recommended Dosage for Healing of Erosive Esophagitis	Recommended Dosage for Treatment of *H. pylori* infection
Child-Pugh Class A	20 mg once daily	20 mg twice daily
Child-Pugh Class B	10 mg once daily	Use is not recommended
Child-Pugh Class C	10 mg once daily	Use is not recommended

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

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Approval Criteria		
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Current age ≥ 21 years: Pass to RPh; deny, not funded by OHP. Current age < 21 years: Go to #3
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the diagnosis for erosive esophagitis?	**Yes:** Go to #6	**No:** Go to #7
6. Has the patient tried an 8-week course of a proton pump inhibitor (e.g. lansoprazole, pantoprazole), and do they still have symptoms of erosive esophagitis?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the indication for treatment of *Heliobacter pylori*?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Have baseline renal function tests been obtained?	**Yes:** Go to #9 and document results_____	**No:** Pass to RPh. Deny; medical appropriateness
9. Is estimated glomerular filtration rate < 30 mL/min?	**Yes:** Go to #10	**No:** Go to #11
10. If the indication is for healing of erosive esophagitis, is the dose of vonoprazan 10 mg once a day?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness

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Approval Criteria		
11. Does the patient have hepatic impairment?	**Yes:** Go to #12	**No:** Approve for the recommended duration of therapy based upon indication. • Treatment of H. pylori infection: 2 weeks • Healing of erosive esophagitis: 8 weeks
12. Has the vonoprazan dose been adjusted for indication and level of hepatic impairment as outlined in **Table 1**?	**Yes:** Approve for the recommended duration of therapy based upon indication. • Treatment of H. pylori infection: 2 weeks • Healing of erosive esophagitis: 8 weeks	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request to maintain healing of erosive esophagitis and to provide relief of heartburn associated with erosive esophagitis?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Is the vonoprazan dose 10 mg once a day?	**Yes:** Approve for up to 24 weeks (6 months).	**No:** Pass to RPh. Deny; medical appropriateness.

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