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Drug Class Literature Scan: Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Date of Review: May 2017

Date of Last Review: March 2015
Literature Search: 02/27/17 – 03/03/17

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

Conclusions:

- A literature scan identified six systematic reviews and meta-analyses[1–7], three guidelines[8–10], one new formulation[11] and one expanded indication[11]. There were no specific studies on Medicaid programs. Evidence for subpopulations were identified for patients with cystic fibrosis (CF) and pregnant women.[5,6]
- In patients with functional dyspepsia (FD), proton pump inhibitor (PPI) therapy was associated with resolution of dyspepsia symptoms in 30% of patients compared to 25% of placebo treated patients based on the findings of a recent Cochrane Review (number needed to treat for an additional beneficial outcome [NNTB] was 13 over 2 to 8 weeks).[1] Treatment with PPIs were associated with 33% of patients reporting no symptoms of dyspepsia compared with 26% of H2 receptor antagonist (H2RA) treated patients with a NNTB of 13 based on 2 trials of 2 to 8 weeks duration.[1]
- For erosive esophagitis, one systematic review and meta-analysis found esomeprazole 40 mg and 20 mg to be more effective than omeprazole 20 mg, with NNTs of 17 and 30, respectively.[3] Helicobacter pylori (H. pylori) eradication rates, as part of combination therapy, were similar between esomeprazole 40 mg and 20 mg and omeprazole 20 mg.
- The role of H. pylori in gastric ulcers and cancer make it a target for therapeutic intervention. A high quality systematic review evaluated standard triple therapy (STT), which consists of a PPI, clarithromycin and amoxicillin, compared to non-bismuth quadruple sequential therapy (SEQ) of two phases, the first induction phase (amoxicillin and a PPI for 5 days) followed by a triple regimen phase (PPI, clarithromycin and metronidazole for 5 days).[2] The analysis found SEQ regimens to eradicate H. pylori 82% of the time compared to 75% in the STT group (RD 0.09; 95% CI, 0.06 to 0.11; $p < 0.001$; ARR 7%; NNT 14); however, when trials from 2008 and later were considered there was no longer a benefit of SEQ treatment over STT.[2]
- A comparison of esomeprazole and omeprazole for the treatment of GERD was done in a systematic review and meta-analysis of good quality.[4] Esophageal healing rates were found to be similar for esomeprazole and omeprazole when used at equivalent doses. Esomeprazole 40 mg was found to be more effective than omeprazole 20 mg on esophageal healing rates (ARR 6%; NNT 17). There was no evidence for comparisons between esomeprazole 40 mg and omeprazole 40 mg. Relief of GERD symptoms were similar between esomeprazole and omeprazole when used at equivalent doses.[4]
- Evidence for the use of PPIs and H2RAs in subpopulations were available for patients with CF and pregnant women.[5,6] There was insufficient evidence to suggest that therapies that lower gastric acidity have conclusive benefits in patients with CF.[5] Medical treatment with intramuscular (IM) prostigmine, magnesium sulfate, aluminum hydroxide, simethicone and sucralfate were found to relieve heartburn symptoms more than placebo in pregnant women.[6]

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- Guidelines from the American College of Gastroenterology on management of H. pylori support the use of a PPIs in H. pylori treatment regimens.[8] No preference of specific PPI was recommended.
- The National Institute for Health and Care Excellence (NICE) published a guidance on the management of infants, children and young people with GERD, in which PPI or H2RA therapy were recommended equally.[10] Choice of therapy should be based on age-appropriate formulation, patient or caregiver preference and cost.[10]
- Dexlansoprazole SoluTabs (Dexilant) was approved in January of 2016 based on evidence from previous studies of dexlansoprazole delayed-release capsules.[11]

Recommendations:
- Recommend adding dexlansoprazole SoluTabs to the current prior authorization (PA) criteria for PPIs. Clarify intent of the PPI PA criteria by making minor modifications to the wording. (Appendix 4)
- No further research is needed at this time. After evaluation of comparative costs in the executive session, make ranitidine 150mg tablets, ranitidine 300mg tablets, famotidine 20mg tablets, and famotidine 40mg tablets preferred.

Previous Conclusions:
- There is high quality evidence that there is no difference in effectiveness between PPIs for healing and maintaining remission of erosive gastro-esophagitis based on endoscopy, relieving symptoms of heartburn for up to 8 weeks, or treatment of PUD or NSAID-induced ulcers.
- There is high quality evidence that there is no difference in efficacy between H2RAs for the management of gastro-esophageal reflux or GERD.
- There is moderate quality evidence that there are no differences in harms between different PPIs or between H2RAs. In general, long-term use of PPIs are associated with severe adverse effects that are not associated with H2RAs
    - No association between outpatient use of H2RAs and risk for *Clostridium difficile*-associated diarrhea was found; this evidence conflicts with previous evidence that suggested an association with chronic PPI use does exist.
    - Patients on long-term PPI therapy should receive an annual re-evaluation to determine need for continued therapy secondary to increased harms, including osteoporosis, *Clostridium difficile*–associated diarrhea and certain nutritional deficiencies. However, the accumulating evidence from better designed, prospective clinical studies cannot substantiate the initial concerns for adverse cardiovascular effects of PPI use in patients on clopidogrel originally seen in the retrospective cohort studies.
- There is high quality evidence that there is no difference between long-term treatment of PPIs and short-term treatment of PPIs for erosive gastro-esophagitis based on endoscopy.
- There is insufficient evidence for long-term treatment of PPIs for symptomatic GERD as most studies evaluating PPIs for the management of GERD are limited to 8 weeks' duration.
- There is insufficient evidence to suggest long-term PPI use significantly decreases incidence of esophageal adenocarcinoma and/or high-grade dysplasia in patients with Barrett's esophagus. The role of PPIs in Barrett's esophagus remains uncertain due to conflicting observational data.
- There is moderate quality evidence that there is no difference in safety or efficacy between PPIs in managing symptoms of reflux in the pediatric population aged 1 year and older. Evidence for use of H2RAs is limited to ranitidine. There is insufficient evidence for use of these agents in infants.
- Low quality evidence suggests PPIs and H2RAs in Cystic Fibrosis patients improves gastrointestinal symptoms and fat absorption but there is insufficient evidence of their effect on nutritional status, lung function, quality of life or mortality.

Previous Recommendations:

- Use current evidence and data presented in the PPI/H2RA Drug Use Evaluation to guide new PA criteria.
- Evaluate comparative drug costs for both classes in the executive session.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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.

New Systematic Reviews:

Cochrane: PPIs for Functional Dyspepsia

A 2017 Cochrane Review focused on the evidence for the use of PPIs for the improvement in dyspepsia symptoms and quality of life when used in patients with functional dyspepsia (FD).[1] Comparators included placebo, H2RAs or prokinetics. Twenty-three randomized controlled trials in patients 16 years and older with a diagnosis of FD were included. Follow-up lasted from 2-8 weeks. Low and high dose PPIs had similar efficacy and therefore these groups were combined. Global symptoms of dyspepsia or epigastric pain/discomfort was the main outcome of interest.

PPI therapy was associated with no or minimal symptoms of dyspepsia in 30% percent of patients compared with 25% of patients taking placebo based on data from 16 trials (RR 0.88; 95% CI, 0.82 to 0.94; ARR 5%; NNT 13) (based on moderate quality of evidence).[1] The number needed to treat for an additional beneficial (NNTB) outcome was 13. When PPIs were compared to H2RAs, PPI treatment resulted in no symptoms in 33% of patients compared to 26% of placebo treated patients with a NNTB of 13, based on 2 studies (RR 0.88; 95% CI, 0.74 to 1.04).[1] Similar evidence was found for PPI and prokinetic comparisons, where PPIs were more effective (RR 0.90; 95% CI, 0.81 to 1.00). The combination regimen of PPI and prokinetics were more effective at reducing symptoms of dyspepsia compared to PPIs alone. The evidence ranged from low to moderate in quality.

Cochrane: Sequential vs. Standard Triple First-line Therapy for H. Pylori Eradication

The focus of this review is to compare standard triple therapy (STT) with a newly recommended non-bismuth quadruple sequential therapy (SEQ) on the eradication rates for H. pylori.[2] The STT regimen consists of a PPI, clarithromycin and amoxicillin compared to the SEQ regimen of two phases, the first induction phase (amoxicillin and a PPI for 5 days) followed by a triple regimen phase (PPI, clarithromycin and metronidazole for 5 days). Randomized controlled trials evaluating 10 days of SEQ to STT (of at least 7 days) in adults and children with an H. pylori diagnosis were included. Forty-four trials (n=12,284) were included.[2]

Trials found SEQ to eradicate H. pylori 82% of the time compared to 75% in the STT group (risk difference [RD] 0.09; 95% CI, 0.06 to 0.11; $p < 0.001$).[2] High heterogeneity ($I^2 = 75\%$) and no difference between treatment in 20 of the trials, weakens the strength of the evidence for this outcome. Subgroup analysis of studies from 2008 and later found no difference between SEQ and STT regimens. Use of STT regimens for 14 days produced equivalent outcomes to SEQ regimens. Very low quality evidence in patients with clarithromycin resistance found SEQ to be effective in 75% of patients compared to 43% with STT.[2] Adverse events occurred in 20.4% of patients taking SEQ compared with 19.5% taking STT (RD 0.00; 95% CI, -0.02 to 0.02). Overall evidence was limited by lack of trial methodology reporting. Both SEQ and STT failed to meet desired eradication rates of ≥ 90%.

Esomeprazole vs. Omeprazole for GERD, PUD and H. Pylori Eradication

A systematic review and meta-analysis analyzed RCTs that compared omeprazole to esomeprazole in adult patients (18 and over) with PUD, GERD or H. pylori infection. Fifteen RCTs were identified, 7 related to GERD and 8 related to H. Pylori.[3] In trials were the indication for PPI therapy was GERD, the mean age was 45 to 58 years old and the majority (73%) had grade B or C erosive esophagitis based on the Los Angeles classification system. Esomeprazole was given as 20 mg or 40 mg daily compared to omeprazole 20 mg daily. In the trials of H. pylori eradication, the mean age was 39 to 59 years old.[3] Esomeprazole doses in the H. pylori trials were 40 mg twice daily in 3 trials and 20 mg twice daily in 5 trials, with all comparisons to omeprazole 20 mg twice daily. The main outcomes were resolution of GERD-related symptoms, esophagitis healing, peptic ulcer healing, H. pylori eradication, quality of life and adverse effects.

Esomeprazole 40 mg was found to be 6% more effective than omeprazole 20 mg for the healing of esophagitis at week 8 of treatment with a NNT of 17 (RR 1.07; 95% CI, 1.02 to 1.12).[3] Comparisons between esomeprazole 20 mg and omeprazole 20 mg at week 8 also demonstrated 3.3% higher healing rates with esomeprazole (RR 1.04; 95% CI, 1.01 to 1.08; NNT 30). The rates of heartburn resolution were 64% to 68% for esomeprazole 40 mg and 57% to 63% for patients taking omeprazole 20 mg. The efficacy between esomeprazole 20 mg and omeprazole 20 mg for H. pylori eradication was similar (RR 1.01; 95% CI, 0.96 to 1.05) and for esomeprazole 40 mg compared to omeprazole 20 mg (RR 1.16; 95% CI, 1.01 to 1.32).[3] Eradication rates ranged from 70-96% for esomeprazole (20 mg and 40 mg doses) and 65-88% for omeprazole. A subgroup analysis found that esomeprazole 40 mg was not more effective than omeprazole 20 mg at week 8 in participants in eastern Asia. There was insufficient data on comparisons between omeprazole and esomeprazole in PUD. Adverse events were similar between treatments.

Comparative Efficacy and Tolerability Between Esomeprazole and Omeprazole for GERD

Esomeprazole and omeprazole are commonly used treatments for GERD. This systematic review and meta-analysis was done to evaluate the efficacy and tolerability of omeprazole when used for the treatment of GERD in adults (18 years and over).[4] Ten randomized controlled trials (n=10,286) graded as high quality were included. Main outcome measures were healing rate (determined by endoscopic evaluation), GERD related symptom relief and tolerability (defined by withdrawal rates). Patients who had secondary GERD due to asthma, chronic cough, or laryngitis or GERD due to laryngopharyngeal reflux disease and trials of duplicate or un-extractable data were not included.

Healing rates were 87% for esomeprazole (20 and 40 mg doses combined) compared to 82% for omeprazole with a RR of 1.0564 (95% CI, 1.0128 to 1.1018; p=0.01; ARR 5%, NNT=20).[4] Healing rate comparisons between esomeprazole 20 mg and omeprazole 20 mg were similar (RR 1.0363; 95% CI, 0.9997 to 1.0743). Esomeprazole 40 mg healed 88% of patients compared to 82% of those treated with omeprazole 20 mg (RR 1.0690; 95% CI, 1.0043 to 1.1380; p = 0.001; ARR 6%, NNT 17).[4] For symptoms relief only the comparison between esomeprazole 20 mg and omeprazole 40 mg demonstrated significant differences between groups. Esomeprazole 20 mg was associated with 46% of patients obtaining relief from GERD symptoms compared to 68% in the omeprazole 20 mg group (ARR 22%, NNT 5). Tolerability was found to be similar between esomeprazole and omeprazole (RR 1.07; 95% CI, 0.88 to 1.30; p = 0.47).[4] Overall, esophageal healing was increased

when higher doses were used but not different at equivalent doses of therapy. Esomeprazole 40 mg had the highest healing rates but there were no comparisons to omeprazole 40 mg. Relief of GERD symptoms did not mirror healing rates and the only difference was found when omeprazole was used at a higher dose than esomeprazole.

Cochrane: Deprescribing versus Continuation of Chronic Proton Pump Inhibitor Use in Adults

The effects of deprescribing long-term use of PPI treatment compared to chronic daily use, defined as 28 days or longer, was evaluated.[7] Deprescribing involves gradually reducing therapy or stopping treatment in an effort to reduce overutilization of medication that is no longer indicated. Trials enrolling patients over the age of 18 with a diagnosis of GERD, functional dyspepsia, PUD, H. pylori, esophageal stricture or Barrett's esophagus were included. Six RCTs (n=1758) were identified that met the inclusion criteria of PPI discontinuation or decreased dosage, with or without the addition of an H2RA. Five trials evaluated on-demand therapy and one trial abruptly discontinued PPI therapy.[7] Trial durations were 13 weeks to 6 months in length and included the following PPIs: pantoprazole 20 mg, rabeprazole 10 mg and 20 mg and esomeprazole 20 mg. The majority of patients were 48-57 years of age and one trial enrolled patients with a mean age of 73. Patients were diagnosed with nonerosive reflux disease or mild forms of esophagitis as indicated by LA grade A or B. None of the trials were conducted in the United States (US). Lack of symptom control (heartburn, regurgitation, dyspepsia, epigastric pain, nausea, bloating and belching) was the primary outcome.

Trials that evaluated continuous PPI use compared to on-demand PPI use found a 9.2% incidence of lack of symptom control in the continuous group compared to 16.3% of the participants in the on-demand group (RR 1.71; 95% CI, 1.31 to 2.21), based on low quality of evidence.[7] Moderate quality of evidence found the amount of PPI taken each week was less with those taking on-demand PPIs compared to continuous therapy (MD -3.79; 95% CI -4.73 to -2.84).[7] Adverse events were only reported in two trials. The incidence of esophagitis and relapse rates of esophagitis was higher in patients treated with the on-demand dosage regimen. Satisfaction with PPI therapy was lower in patients taking on-demand dosing compared to continuous dosing based on very low quality evidence. External validity is low since no patients were from US sites. Small sample sizes and unclear to high risk of bias in a majority of the trials prevents strong conclusions.

<u>Subpopulations</u>

Cochrane: Drug Therapies for Gastric Acid Reduction in People with Cystic Fibrosis

A 2016 Cochrane Review evaluated the effect of drug therapies that reduce gastric acidity in adults and children with cystic fibrosis (CF).[5] Thirteen trials included placebo comparisons to PPIs (6 trials) and H2RAs (7 trials). The other trials conducted the following comparisons: PPIs vs. H2RAs vs. placebo; pancrelipase vs. pancrelipase and misoprostol; misoporstil vs. placebo; enprostil (not available in the US) vs. ranitidine; sodium bicarbonate vs. placebo; sodium bicarbonate vs. calcium carbonate.[5] Outcomes of interest were: nutritional status, symptoms associated with gastric acidity, fat absorption, lung function, quality of life and survival. Seventeen trials were included but not enough data was provided for a meta-analysis. Risk of bias and study quality was not able to be accessed due to lack of trial methodology. Very limited evidence from one trial with misoprostol suggests improvement in symptoms of abdominal pain in patients with CF. Misoprostol, omeprazole, cimetidine, ranitidine and sodium bicarbonate were found to improve measures of fat malabsorption based on low quality evidence. Additional high-quality evidence is needed to determine the benefits of gastric acid reduction in patients with CF.

Cochrane: Interventions for Heartburn in Pregnancy

Interventions to treat heartburn in pregnancy were the focus of a Cochrane Review.[6] Randomized controlled trials of diet, lifestyle modifications, PPIs, H2RAs, antacids and promotility drugs were included. Evidence was available for the following pharmaceuticals: prostigmine, combination of magnesium sulfate, aluminum hydroxide and simethicone and sucralfate. The primary outcome was complete heartburn relief.

Four trials (n=358) were identified. Two trials evaluated the effects of pharmaceutical therapy, using IM prostigmine 0.5 mg compared to placebo and magnesium sulfate, aluminum hydroxide and simethicone combination compared to placebo.[6] Complete heartburn relief was more common in patients receiving medical treatment versus placebo (RR 1.85; 95% CI, 1.36 to 2.50) (moderate quality evidence). Evidence on partial relief of heartburn and adverse events were found to be similar between groups and was based on very low quality of evidence. One small trial found sucralfate, 1 g three times daily, was found to be more effective than dietary and lifestyle interventions (not described) for complete heartburn relief (RR 2.41; 95% CI, 1.42 to 4.07).[6] There was insufficient evidence for the outcomes of miscarriage, preterm labor, material satisfaction, fetal abnormalities, intrauterine growth restriction or low birthweight.

New Guidelines:

American College of Gastroenterology: Treatment of H. Pylori

In a 2017 guideline update the *American College of Gastroenterology (ACG)* outlined recommendations for the treatment of H. pylori updating its 2007 recommendations.[8] The quality of the study was assessed according to the GRADE methodology (very low to high) and recommendations were considered strong or conditional based on this evidence. Table 1 outlines indication for treatment of H. pylori and Table 2 outlines treatment recommendations. History of antibiotic use should be obtained from the patients before recommending treatment regimen. Testing to prove eradication should be done after treatment or H. pylori with a urea breath test, fecal antigen test or biopsy-based testing at least 4 weeks after completion of antibiotic therapy and at least 1-2 weeks after withholding PPI treatment. If treatment with one of the first-line options fail, additional regimens should avoid containing antibiotics that have been taken previously by the patient (strong recommendation; moderate quality of evidence).[8] Local antimicrobial resistance patterns should be taken into account when recommending salvage regimens. Bismuth quadruple therapy or levofloxacin salvage regimens are the preferred therapy for patients previously receiving a regimen containing clarithromycin. If the patient received bismuth quadruple therapy the recommendation is for clarithromycin or levofloxacin-containing salvage regimens. Clarithromycin triple therapy should not be used as salvage regimen. Table 3 outlines salvage regimen options.

Table 1. Indications for treatment of H. Pylori[8]

Indication	Strength of recommendation/ quality of evidence
Patients with known H. pylori infection based on gastric biopsy during upper endoscopy in patients with dyspepsia	Strong/ high
Patients with symptoms of GERD who test positive for H. pylori (effect on GERD symptoms are unpredictable)	Strong/ high
Patients taking long-term, low-dose aspirin therapy who test positive for H. pylori to reduce risk of ulcer bleeding	Conditional / moderate
Patients who will be starting chronic NSAIDs and test positive for H. pylori	Strong / moderate
Testing and treating patients for H. pylori who are already taking NSAIDs	Conditional / low
Patients with unexplained iron deficiency anemia and who test positive for H. pylori	Conditional / low
Adults with idiopathic thrombocytopenic purpura (ITP) and who test positive for H. pylori	Conditional / very low

Table 2. H. Pylori Treatment Recommendations[8]

First-line Treatment Options	Strength of recommendation / quality of evidence
Clarithromycin triple therapy – Clarithromycin, a PPI, and amoxicillin or metronidazole for 14 days*	Conditional / low (for duration of treatment: moderate)
Bismuth quadruple therapy – PPI, bismuth, tetracycline and a nitroimidazole for 10-14 days (good option for patients with a penicillin allergy and previous macrolide exposure)	Strong / low
Concomitant therapy - PPI, clarithromycin, amoxicillin and a nitroimidazole for 10-14 days	Strong / low (for duration of treatment: moderate)
Sequential therapy - PPI and amoxicillin for 5-7 days followed by a PPI, clarithromycin, and a nitroimidazole for 5-7 days	Conditional / low (for duration of treatment: very low)
Hybrid therapy - PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin, and a nitroimidazole for 7 days	Conditional / low (for duration of treatment: very low)
Levofloxacin triple therapy – PPI, levofloxacin and amoxicillin for 10-14 days	Conditional / low (for duration of treatment: very low)
Fluoroquinolone sequential therapy – PPI and amoxicillin for 5-7 days followed by a PPI, fluoroquinolone and nitroimidazole for 5-7 days	Conditional / low (for duration of treatment: very low)
* In regions where resistance is low (< 15%) and in patients with no history of previous history of macrolide exposure for any reason	

Table 3. Salvage Treatment for First-line Therapy Failures[8]

Salvage Regimen	Strength of recommendation / quality of evidence
Bismuth quadruple therapy for 14 days	Strong / low
Levofloxacin triple regimen for 14 days	Strong / moderate (for treatment duration: low)
Concomitant therapy for 10-14 days	Conditional / very low
Rifabutin triple regimen – PPI, amoxicillin and rifabutin for 10 days	Conditional / moderate (for treatment duration: very low)
High-dose dual therapy – PPI and amoxicillin for 14 days	Conditional / low (for treatment duration: very low)

NICE: GERD in Children and Young People

In a 2015 update, NICE updated recommendations for the treatment for GERD in infants (less than 1 year), children (1-12 years) and young (12-18 years) people.[10] Guidelines do not recommend treatment of regurgitation with PPIs or H2RAs in infants and children if it occurs as an isolated symptom. Metoclopramide, droperidone or erythromycin should be used for gastro-esophageal reflux or GERD only after consultation with a specialist to weigh risks and benefits. A trial lasting 4 weeks of a PPI or H2RA should be considered in patients who are unable to verbalize symptoms who have overt regurgitation and one of the following:

- Unexplained feeding difficulties
- Distressed behavior
- Faltering growth

PPI and H2RAs can also be used for a 4-week trial in children and young people with persistent heartburn, retrosternal or epigastric pain.[10] Consultation with a specialist for a possible endoscopy should be considered for patients that continue to have symptoms after a 4-week trial or who have reoccurrence of symptoms after stopping treatment. Patients who have endoscopy proven reflux esophagitis should be considered for repeat endoscopic evaluation to guide future treatment. Choice of treatment between PPIs and H2RAs should be dependent upon the availability of age-appropriate preparations, the preference of patient or caregiver and cost.[10]

CHEST: Treatment of Unexplained Chronic Cough

A systematic review of randomized trials was done to provide recommendations for the management of unexplained chronic cough. Trials of patients twelve and older with a chronic cough lasting more than 8 weeks with no causative explanation were included. Trials were graded for quality and incorporated into guideline recommendations. For the purpose of this review, only recommendations pertaining to PPIs and H2RAs will be included. The evidence found no benefit of PPI therapy on cough severity or quality of life in adult patients without a history of acid gastroesophageal reflux disease based on one trial with high-dose esomeprazole (weak recommendation based on low to very-low quality of evidence).

New Formulations:

In January of 2016 a new form of dexlansoprozole, Dexilant SoluTab, was approved.[11] This delayed-release orally disintegrating tablet (DT) is indicated for the maintenance of healed erosive esophagitis (EE) and relief of heartburn and treatment of symptomatic non-erosive GERD in patients 12 and over. The dexlansoprozole SoluTab is not recommended for the healing of EE. The dose is given as one 30 mg SoluTab at least 30 minutes before a meal. Two 30 mg dexlansoprozole SoluTabs are not interchangeable with one 60 mg dexlansoprozole oral capsule and therefore there is no evidence for the efficacy of dexlansoprazole SoluTabs in EE healing and they are not recommended for this indication.

In July of 2016 dexlansoprazole capsules obtained the indication for use in pediatric patients 12-17 years old for healing all grades of EE.[11] Both dexlansoprazole capsules and dexlansoprazole DT received approval for use in pediatric patients 12-17 years for maintenance of healed EE and relief of heartburn and treatment of heartburn associated with symptomatic non-erosive GERD.

New FDA Safety Alerts: No new safety alerts identified.

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10. National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease in children and young people: diagnosis and management. 2015. nice.org.uk/guidance/ng1.

11. Dexilant (dexlansoprazole delayed-release capsules), Dexilant Solu Tabs (dexlansoprazole delayed-release orally disintegrating tablets). Takeda Pharmaceuticals America, Inc. Deerfield, IL.

Appendix 1: Current Preferred Drug List

Proton Pump Inhibitors:

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE DR	OMEPRAZOLE	OMEPRAZOLE	Y
ORAL	CAPSULE DR	PRILOSEC	OMEPRAZOLE	Y
ORAL	TABLET DR	PANTOPRAZOLE SODIUM	PANTOPRAZOLE SODIUM	Y
ORAL	TABLET DR	PROTONIX	PANTOPRAZOLE SODIUM	Y
ORAL	CAP DR BP	DEXILANT	DEXLANSOPRAZOLE	N
ORAL	CAP DR SPR	ACIPHEX SPRINKLE	RABEPRAZOLE SODIUM	N
ORAL	CAPSULE	OMEPRAZOLE-SODIUM BICARBONATE	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	CAPSULE	ZEGERID	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	CAPSULE	ZEGERID OTC	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	CAPSULE DR	ESOMEPRAZOLE MAGNESIUM	ESOMEPRAZOLE MAGNESIUM	N
ORAL	CAPSULE DR	ESOMEPRAZOLE STRONTIUM	ESOMEPRAZOLE STRONTIUM	N
ORAL	CAPSULE DR	HEARTBURN TREATMENT 24 HOUR	LANSOPRAZOLE	N
ORAL	CAPSULE DR	LANSOPRAZOLE	LANSOPRAZOLE	N
ORAL	CAPSULE DR	NEXIUM	ESOMEPRAZOLE MAGNESIUM	N
ORAL	CAPSULE DR	NEXIUM 24HR	ESOMEPRAZOLE MAGNESIUM	N
ORAL	CAPSULE DR	OMEPRAZOLE MAGNESIUM	OMEPRAZOLE MAGNESIUM	N
ORAL	CAPSULE DR	PREVACID	LANSOPRAZOLE	N
ORAL	CAPSULE DR	PREVACID 24HR	LANSOPRAZOLE	N
ORAL	GRANPKT DR	PROTONIX	PANTOPRAZOLE SODIUM	N
ORAL	PACKET	OMEPRAZOLE-SODIUM BICARBONATE	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	PACKET	ZEGERID	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	SUSPDR PKT	NEXIUM	ESOMEPRAZOLE MAGNESIUM	N
ORAL	SUSPDR PKT	PRILOSEC	OMEPRAZOLE MAGNESIUM	N
ORAL	TAB RAP DR	PREVACID	LANSOPRAZOLE	N
ORAL	TABLET DR	ACIPHEX	RABEPRAZOLE SODIUM	N
ORAL	TABLET DR	NEXIUM 24HR	ESOMEPRAZOLE MAGNESIUM	N
ORAL	TABLET DR	OMEPRAZOLE	OMEPRAZOLE	N
ORAL	TABLET DR	PRILOSEC OTC	OMEPRAZOLE MAGNESIUM	N
ORAL	TABLET DR	RABEPRAZOLE SODIUM	RABEPRAZOLE SODIUM	N

Histamine-2 Receptor Antagonists:

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	SYRUP	RANITIDINE HCL	RANITIDINE HCL	Y
ORAL	SYRUP	ZANTAC	RANITIDINE HCL	Y
ORAL	TABLET	ACID CONTROLLER	FAMOTIDINE	Y
ORAL	TABLET	ACID REDUCER	FAMOTIDINE	Y
ORAL	TABLET	ACID REDUCER	RANITIDINE HCL	Y
ORAL	TABLET	FAMOTIDINE	FAMOTIDINE	Y
ORAL	TABLET	HEARTBURN PREVENTION	FAMOTIDINE	Y
ORAL	TABLET	HEARTBURN RELIEF	FAMOTIDINE	Y
ORAL	TABLET	HEARTBURN RELIEF	RANITIDINE HCL	Y
ORAL	TABLET	PEPCID AC	FAMOTIDINE	Y
ORAL	TABLET	RANITIDINE	RANITIDINE HCL	Y
ORAL	TABLET	RANITIDINE HCL	RANITIDINE HCL	Y
ORAL	TABLET	WAL-ZAN 75	RANITIDINE HCL	Y
ORAL	TABLET	ZANTAC 75	RANITIDINE HCL	Y
ORAL	CAPSULE	AXID	NIZATIDINE	N
ORAL	CAPSULE	NIZATIDINE	NIZATIDINE	N
ORAL	CAPSULE	RANITIDINE HCL	RANITIDINE HCL	N
ORAL	ORAL SUSP	FAMOTIDINE	FAMOTIDINE	N
ORAL	ORAL SUSP	PEPCID	FAMOTIDINE	N
ORAL	SOLUTION	AXID	NIZATIDINE	N
ORAL	SOLUTION	CIMETIDINE	CIMETIDINE HCL	N
ORAL	SOLUTION	CIMETIDINE HCL	CIMETIDINE HCL	N
ORAL	SOLUTION	NIZATIDINE	NIZATIDINE	N
ORAL	TAB CHEW	ACID CONTROLLER COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	ACID REDUCER COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	DUAL ACTION	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	DUAL ACTION COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	DUO FUSION	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	PEPCID COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	TUMS DUAL ACTION	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB RAPDIS	PEPCID RPD	FAMOTIDINE	N
ORAL	TABLET	ACID CONTROL	FAMOTIDINE	N
ORAL	TABLET	ACID CONTROL	RANITIDINE HCL	N

ORAL	TABLET	ACID CONTROLLER	FAMOTIDINE	N
ORAL	TABLET	ACID REDUCER	CIMETIDINE	N
ORAL	TABLET	ACID REDUCER	FAMOTIDINE	N
ORAL	TABLET	ACID REDUCER	RANITIDINE HCL	N
ORAL	TABLET	ACID REDUCER 150	RANITIDINE HCL	N
ORAL	TABLET	CIMETIDINE	CIMETIDINE	N
ORAL	TABLET	FAMOTIDINE	FAMOTIDINE	N
ORAL	TABLET	HEARTBURN PREVENTION	FAMOTIDINE	N
ORAL	TABLET	HEARTBURN RELIEF	CIMETIDINE	N
ORAL	TABLET	HEARTBURN RELIEF	FAMOTIDINE	N
ORAL	TABLET	HEARTBURN RELIEF	RANITIDINE HCL	N
ORAL	TABLET	HEARTBURN RELIEF 150	RANITIDINE HCL	N
ORAL	TABLET	PEPCID	FAMOTIDINE	N
ORAL	TABLET	PEPCID AC	FAMOTIDINE	N
ORAL	TABLET	RANITIDINE HCL	RANITIDINE HCL	N
ORAL	TABLET	TAGAMET	CIMETIDINE	N
ORAL	TABLET	TAGAMET HB	CIMETIDINE	N
ORAL	TABLET	WAL-ZAN 150	RANITIDINE HCL	N
ORAL	TABLET	ZANTAC	RANITIDINE HCL	N

Appendix 2: New Comparative Clinical Trials

A total of 292 citations were manually reviewed from the initial literature search. After further review, 282 citations were excluded and no randomized trials were included because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2017
Search Strategy:

#	Searches	Results
1	ranitidine.mp. or Ranitidine/	2787
2	cimetidine.mp. or Cimetidine/	2540
3	famotidine.mp. or Famotidine/	1102
4	nizatidine.mp. or Nizatidine/	189
5	1 or 2 or 3 or 4	5904
6	limit 5 to (english language and humans and yr="2015 -Current")	121
7	limit 6 to (clinical trial or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews)	30
8	omeprazole.mp. or Omeprazole/	7600
9	pantoprozole.mp.	6
10	dexlansoprazole.mp. or Dexlansoprazole/	69
11	esomeprazole.mp. or Esomeprazole/	1126
12	lansoprazole.mp. or Lansoprazole/	2263
13	rabeprazole.mp. or Rabeprazole/	1062
14	8 or 9 or 10 or 11 or 12 or 13	9501
15	limit 14 to (english language and humans and yr="2015 -Current")	443
16	limit 15 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	171

Author: Sentena

Date: May 2017

Appendix 4: Prior Authorization Criteria

Proton Pump Inhibitors (PPIs)

Goals:

- Promote PDL options
- Restrict PPI use to patients with OHP-funded conditions

Requires PA:

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

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at
- 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 #5	**No:** Go to #3
3. Is the treating diagnosis an OHP-funded condition (see **Table**)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by OHP.
4. 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 Committee.	**Yes:** Inform prescriber of covered alternatives.	**No:** Go to #5
5. Has the patient already received 68 days of PPI therapy 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 #6	**No:** Go to #7
6. Does the patient have recurrent, symptomatic erosive esophagitis that has resulted in previous emergency department visits or hospitalizations?	**Yes:** Approve for 1 year	**No:** Go to #7
7. Does the patient have a history of gastrointestinal ulcer or bleed and have one or more of the following risk factors? • Age 65 years or older • Requires at least 3 months of continuous daily: i. Anticoagulant; ii. Aspirin or non-selective NSAID; or iii. Oral corticosteroid	**Yes:** Approve for 1 year	**No:** Go to #8

8. 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 or not funded by OHP 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.

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

Funded OHP Conditions*	Maximum Duration	Maximum Daily Dose
GERD: Esophagitis (K20.0-K20.9) Esophageal reflux (K21.0-K21.9)	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	2 weeks	
Achalasia and cardiospasm Barrett's esophagus with dysplasia Stricture and stenosis of esophagus Perforation of esophagus Dyskinesia of esophagus Gastroesophageal laceration-hemorrhage syndrome Esophageal hemorrhage Gastric ulcer Duodenal ulcer Peptic ulcer Gastrojejunal ulcer Gastritis and duodenitis Zollinger-Ellison Neoplasm of the thyroid or parathyroid gland Malignant mast cell tumors Multiple endocrine neoplasia [MEN] type I	1 year	Dexlansoprazole 60 mg Dexlansoprazole 30 mg† Esomeprazole 40 mg Lansoprazole 60 mg Omeprazole 40 mg Pantoprazole 80 mg Rabeprazole 40 mg

*A current list of funded conditions is available at: http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx

† Dexlansoprazole SoluTab 30 mg (given as 2 SoluTabs at once) are not recommended for healing of erosive esophagitis.

P&T / DUR Review: *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: *6/8/16; 4/15; 5/13; 5/12; 1/11; 4/10; 1/10; 9/06, 7/06, 10/04, 3/04*