

## **Indiana Medicaid Therapeutics Committee** **Therapeutic Class Review Summary**

### **Therapeutic Class:**

Antiulcer *H. pylori* Agents

### **Overview:**

The single most common cause of peptic ulcer disease (PUD) is infection with *Helicobacter pylori*, a gastrointestinal bacterium. The discovery of the residence of *Helicobacter pylori* in areas of mucosal ulceration has drastically changed the approach to prevention, diagnosis, and treatment of PUD. Conventional therapy with antisecretory agents alone is effective in healing peptic ulcers, and continued low-dose maintenance therapy reduces recurrences to roughly 20% per year. However, the use of accepted antibiotic regimens for *H. pylori* eradication in *H. pylori*-positive patients eradicates the infection, heals the infection-related ulcer, and also decreases the incidence of ulcer related complications. Therapy also reduces the risk of non-NSAID-related recurrence to 10% or less per year. (NSAID = non-steroidal anti-inflammatory drug)

The 2007 practice guidelines of the American College of Gastroenterology (ACG) recommend the use of treatment regimens that have achieved eradication rates of 70-90%. Combination drug regimens are essential to maximize the eradication rate and minimize the risk of promoting antimicrobial resistance. Triple or quadruple regimens are most effective; however, ACG reports that eradication rates with both are declining. Additional factors to consider when selecting a treatment regimen are antibiotic resistance, compliance/complexity of regimen, and likelihood of adverse effects. The following regimens are recommended by ACG for the treatment of *H. pylori* infection:

- A proton pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole for 10-14 days
- Bismuth subsalicylate, metronidazole, tetracycline, and either ranitidine or PPI for 10-14 days
- A PPI plus amoxicillin for 5 days followed by PPI, clarithromycin, and tinidazole for 5 days

The first course of therapy offers the greatest chance of eradication and is the primary recommended therapy in the U.S., with clinical studies reporting an intent-to-treat (ITT) eradication rate of 70-80%. Bismuth based quadruple therapy has achieved ITT eradication rates of 75-90%, and is typically recommended for penicillin allergic patients. The third regimen, used in Europe,

requires validation in the U.S. before it can be recommended as first-line therapy. Previously, clinical studies have demonstrated equivalent efficacy of 7-day regimens versus 14-day regimens; however, a recent large single center trial in Europe, and a meta analysis involving over 900 patients, have both demonstrated superiority of 14-day therapy. ACG recommends a 14-day course of clarithromycin based therapy. Shorter durations of therapy have been typically used in the U.S. (7-10 days) where eradication rates are  $\leq 80\%$ .

Three *H. pylori* eradication therapies are available in the US. Helidac<sup>®</sup> is comprised of bismuth subsalicylate chewable tablets, metronidazole tablets, and tetracycline capsules. Pylera<sup>™</sup> is available as a capsule, which contains bismuth subcitrate potassium, metronidazole, and tetracycline. Both bismuth subsalicylate and bismuth subcitrate potassium disrupt the cell wall of the *Helicobacter pylori* organism. Metronidazole disrupts the organism's DNA and inhibits bacterial nucleic acid synthesis, which eventually leads to cellular death. Tetracycline binds to the 30-S ribosomal subunit in the bacterial cell and prevents binding of transcription RNA to messenger RNA. Helidac<sup>®</sup> therapy is used in combination with an antisecretory agent (H<sub>2</sub> antagonist or a PPI) as quadruple therapy for the eradication of *H. pylori*. Pylera<sup>™</sup> is also used as quadruple therapy for the eradication of *H. pylori*, but is approved for use in combination with omeprazole only. Prevpac<sup>®</sup>, the third *H. pylori* eradication therapy, is a triple therapy eradication regimen. Prevpac<sup>®</sup> contains Prevacid<sup>®</sup> (lansoprazole) capsules, Trimox<sup>®</sup> (amoxicillin) capsules, and Biaxin<sup>®</sup> (clarithromycin) tablets. Lansoprazole, a PPI, inhibits gastric acid secretion by inhibiting the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme system of gastric parietal cells. Amoxicillin inhibits the third and final stage of bacterial wall synthesis, ultimately leading to cell lysis. Clarithromycin, a macrolide antibiotic, binds to the 50-S subunit of the 70-S ribosome thereby blocking RNA-mediated bacterial protein synthesis. Each of the components of Helidac<sup>®</sup> and Prevpac<sup>®</sup> are packaged together in an effort to improve compliance with therapy. The ingredients for Pylera<sup>™</sup> are combined in one capsule.

In clinical studies comparing the efficacy of various triple and quadruple regimens, all proton pump inhibitors can be dosed to perform with equivalent efficacy when the same antibiotic combination is administered. In some studies, high-dose H<sub>2</sub> antagonists have demonstrated equivalent efficacy to PPIs.

Brand Name	Components	Manufacturer
Helidac <sup>®</sup>	Bismuth subsalicylate 262.4-mg chewable tablets, metronidazole 250-mg tablets, and tetracycline 500-mg capsules	Prometheus Laboratories
Prevpac <sup>®</sup>	Prevacid <sup>®</sup> (lansoprazole) 30-mg capsules, Trimox <sup>®</sup> (amoxicillin) 500-mg capsules, and Biaxin <sup>®</sup> (clarithromycin) 500-mg tablets	Tap Pharmaceuticals
Pylera <sup>™</sup>	Capsules containing 140 mg bismuth subcitrate potassium, 125 mg metronidazole, and 125 mg tetracycline hydrochloride	Axcan Pharma, Inc.

**Summary:**

Products in this class are comprised of agents that are packaged together in an effort to improve compliance with H. pylori eradication treatments. However, the ingredients for Pylera<sup>™</sup> are combined in one capsule. Agents that are available generically (omeprazole, famotidine, ranitidine, amoxicillin, metronidazole and bismuth subsalicylate) have demonstrated equivalent efficacy with brand name agents in this class (Prevacid<sup>®</sup>, Trimox<sup>®</sup>, and Biaxin<sup>®</sup>). The proton pump inhibitors on the Preferred Drug List, generic availability, and total cost impact should be taken into consideration when determining preferred drug list status for the agents in this class.