

H. pylori Treatment Review

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***H. pylori* Treatment Review**

FDA-approved combination products^{1,2,3}

Drug	Manufacturer	Indication
bismuth subsalicylate, metronidazole, tetracycline (Helidac [®])	Prometheus	Components are indicated in combination with an H ₂ antagonist for the treatment of patients with <i>Helicobacter pylori</i> infection and duodenal ulcer disease to eradicate <i>H. pylori</i> .
lansoprazole, amoxicillin, clarithromycin (Prevpac [®])	Takeda	Components are indicated for the treatment of patients with <i>H. pylori</i> infection and duodenal ulcer disease to eradicate <i>H. pylori</i> .
bismuth subcitrate potassium, metronidazole, tetracycline (Pylera [®])	Axcan Pharma	Components are indicated in combination with omeprazole for the treatment of patients with <i>H. pylori</i> infection and duodenal ulcer disease to eradicate <i>H. pylori</i> . Omeprazole should be taken with the breakfast dose and dinner dose of Pylera.

Overview

Although the traditional theories regarding the pathogenesis of peptic ulcers focus on acid hypersecretion, this finding is not universal, and it is now known that hypersecretion is not the primary mechanism by which most ulceration occurs. It appears that certain factors, such as *Helicobacter pylori* and NSAIDs, disrupt the normal mucosal defense and repair, making the mucosa more susceptible to the attack of acid.

The mechanisms by which *H. pylori* causes mucosal injury are not entirely clear, but several theories have been proposed. Urease produced by the organism catalyzes urea to ammonia. Ammonia, while enabling the organism to survive in the acidic environment of the stomach, may erode the mucous barrier, leading to epithelial damage. Cytotoxins produced by *H. pylori* have also been implicated in host epithelial damage. Mucolytic enzymes (e.g., bacterial protease, lipase) appear to be involved in degradation of the mucous layer, making the epithelium more susceptible to acid damage. Lastly, cytokines produced in response to inflammation may play a role in mucosal damage and subsequent ulcerogenesis.

H. pylori is associated with intestinal-type adenocarcinoma of the gastric body and antrum. Infected persons are three to six times more likely to develop stomach cancer. Gastric lymphomas and mucosa-associated lymphoma tissue (MALT) lymphomas have also been linked to this infection.⁴ As many as two-thirds of high-grade MALT lymphomas may respond to antibiotic therapy for *H. pylori*.⁵

Eradication of *H. pylori* has been shown to decrease peptic ulcer disease (PUD).⁶ Several studies have shown that eradication of *H. pylori* is more cost-effective than continuous therapy with acid suppression with H₂-antagonists or proton pump inhibitors (PPIs).^{7,8,9} Long-term treatment with H₂-antagonists or PPIs reduces the risk of recurrence proportionally to the amount of acid suppression achieved. One year relapse rate for gastric and duodenal ulcers is

more than 60 percent after cessation of these traditional antiulcer therapies. The rate of ulcer recurrence is considerably lower after *H. pylori* eradication therapy (less than ten percent). Recurrent infections are usually due to persistent *H. pylori*, which, if documented, should be treated with a second course of *H. pylori* eradication therapy.

H. pylori eradication consists of multiple drug therapy that combines antibiotics with an acid-suppressive agent (H₂-antagonists or PPI) for seven to 14 days. Although no regimen offers 100 percent eradication, it appears that dual drug and short-term therapy result in lower eradication rates, compared with triple drug regimens lasting ten to 14 days.^{10,11,12,13,14} Medication compliance, medication-related adverse effects, and antimicrobial resistance may also affect eradication.^{15,16}

The 2007 American College of Gastroenterology (ACG) guidelines recommend 10 to 14 days of a triple-drug regimen containing a proton pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole.¹⁷ Although 10 to 14 days is recommended, ACG also indicates that giving therapy for two weeks may be preferred. In addition, these guidelines state that recent studies suggest that eradication rates achieved by first line therapy with a PPI, clarithromycin and amoxicillin have decreased to 70 to 85 percent, in part due to clarithromycin resistance. Triple therapy using a PPI, clarithromycin and either amoxicillin or metronidazole for 14 days is also recommended as first line therapy in the 2006 global update to the Maastricht III Consensus Report.¹⁸ Bismuth containing quadruple therapy is also a first choice treatment option.

The three packaged combination products available will be included in this review.

Pharmacology

PPIs suppress *H. pylori* and induce rapid ulcer healing. Increased gastric pH accompanying their use can enhance gastric tissue concentration and efficacy of antimicrobials, creating a hostile environment for *H. pylori*.

Bismuth subsalicylate, metronidazole, clarithromycin, and tetracycline individually have demonstrated *in vitro* activity against most susceptible strains of *H. pylori*.¹⁹ Metronidazole resistance occurs most often in patients previously treated with metronidazole, primarily younger women who are more likely to have had prior exposure to the antibiotic.^{20,21,22} Studies have reported *H. pylori* resistance rates to metronidazole of 29.1 to 41 percent.²³ Clarithromycin resistance is not as common (occurrence of 4.1 to 15 percent) and occurs most often in older, female, and inactive ulcer patients.^{24,25} Primary amoxicillin resistance is very rare (1.4 percent).²⁶ Successful eradication of *H. pylori* is affected more by the presence of resistance to clarithromycin than to metronidazole.^{27,28} It would appear that short regimens that include metronidazole may be subject to a reasonably high failure rate, particularly in young women.

In a study of the effect of differing therapies on the development of resistance, dual therapy with the combination of a PPI and clarithromycin resulted in 88.9 percent of the patients acquiring clarithromycin resistance. With triple therapy, percentages of patients acquiring clarithromycin-resistant strains after using PPI + clarithromycin + amoxicillin or PPI + clarithromycin + metronidazole were 38.7 and 90 percent, respectively (p<0.01).²⁹ These data suggest that regimens containing amoxicillin may prevent the selection of secondary clarithromycin resistance.

Pharmacokinetics^{30,31,32}

Pharmacokinetics for both Helidac and Prevpac when all of their components are administered have not been studied. Please consult the individual package inserts for full details.

A comparative pharmacokinetic bioavailability study of Pylera found similar pharmacokinetic parameters for the individual drugs when administered as separate capsule forms or as Pylera. A second pharmacokinetic evaluation showed that food reduces the systemic absorption of all three Pylera components: metronidazole by six percent, tetracycline by 34 percent, and bismuth by 60 percent. The reduction in absorption is not considered to be clinically significant.

Contraindications/Warnings^{33,34,35}

Concomitant administration of Prevpac with any of the following drugs is contraindicated: cisapride, pimozone, astemizole, terfenadine, ergotamine, or dihydroergotamine. There have been post-marketing reports of cardiac arrhythmias and even fatalities as a result of some of the aforementioned drug interactions.

H. pylori treatments may contain a penicillin-type antibiotic. Serious and occasionally fatal anaphylactic reactions have occurred when patients are hypersensitive to penicillins including amoxicillin and even some cephalosporins. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillin therapy. This type of reaction is more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Serious reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids, and airway management, including intubation.

Clarithromycin should not be administered in pregnant women except in clinical circumstances where no alternative treatment option is appropriate.

It should also be noted that regimens and combination products containing metronidazole also carry a black box warning because of its known ability to be carcinogenic in mice and rats. Metronidazole use should be reserved for approved conditions (*H. pylori* being one of them).^{36,37} There is also the added concern of *H. pylori* resistance with metronidazole. It is probably best to reserve combinations containing metronidazole to patients with allergies to clarithromycin or amoxicillin or who have failed therapies with those other antibiotics.

Prescribing any antibiotic-containing *H. pylori* treatment in the absence of a proven or strongly suspected bacterial infection or for a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Helidac is contraindicated in the following patient populations: pregnant or nursing women, pediatric patients, patients with renal or hepatic impairment, and patients with a known hypersensitivity to any of its component ingredients or aspirin/salicylate allergies.

Drug Interactions

All drug interactions are the same as for the individual agents. Consult prescribing information for full details.

Adverse Effects

Drug	Abdominal pain	Diarrhea	Headache	Nausea	Melena	Altered taste
bismuth subsalicylate, metronidazole, tetracycline (Helidac) ³⁸	6.8	6.8	1.5	12	3	nr
lansoprazole, amoxicillin, clarithromycin (Prevpac) ³⁹	<3	7	6	<3	nr	5
bismuth subcitrate potassium, metronidazole, tetracycline (Pylera) + omeprazole ⁴⁰	8.8	8.8	8.2	8.2	nr	4.8

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and should not be considered comparative. nr= not reported.

Special Populations^{41,42,43}

Pediatrics

Effectiveness of a one-week, non-bismuth quadruple therapy was studied prospectively in children with proven *H. pylori* infection in a population with a high rate of metronidazole resistance.⁴⁴ *H. pylori*-positive children were treated with omeprazole, clarithromycin, amoxicillin, and metronidazole for seven days. The result of treatment was assessed one month after treatment with endoscopy and biopsy. The same treatment was repeated for two weeks if *H. pylori* was still present. In patients who needed a third endoscopy, their biopsy specimens were cultured to determine antibiotic sensitivity. Results were correlated with patients' symptoms and endoscopic findings. Thirty-three children with acute (severe epigastric pain, n=14; gastrointestinal bleeding, n=nine) and chronic (recurrent abdominal pain, n=seven; anemia, n=three) conditions were treated for *H. pylori*. Thirty-one (94 percent) were confirmed to have *H. pylori* eradicated by one week of therapy, whereas one patient had eradication after a further two weeks of therapy (3.3 percent). The only unresponsive patient had *H. pylori* isolate resistant to both clarithromycin and metronidazole. All ulcers and erosions healed after the eradication of *H. pylori*. Three patients had persistent recurrent abdominal pain despite *H. pylori* eradication.

Pregnancy

Prevpac is Pregnancy Category C, and Helidac and Pylera are both Pregnancy Category D.

Other considerations – renal, hepatic, race, etc.

Helidac and Pylera combinations are contraindicated in hepatic and renal insufficiency. With severe hepatic insufficiency, a dose reduction of Prevpac is recommended, and its use is not recommended with a creatinine clearance (CrCl) less than 30 mL/min.

Dosages

Drug	Dosage	Additional Medications Required	Duration (days)	Availability
Helidac ⁴⁵	metronidazole 250 mg + tetracycline 500 mg + bismuth subsalicylate 525 mg, each given four times a day	H ₂ receptor antagonist	14	14 blister cards, each containing: -eight bismuth subsalicylate 262.4 mg chewable tablets -four metronidazole 250 mg tablets -four tetracycline 500 mg capsules
Prevpac ⁴⁶	lansoprazole 30 mg + amoxicillin 1 gm + clarithromycin 500 mg, each given twice a day	--	10 or 14	Individual daily administration pack containing: -two lansoprazole 30 mg capsules -four amoxicillin 500 mg capsules -two clarithromycin 500 mg tablets
Pylera ⁴⁷	Each capsule contains: bismuth subcitrate potassium 140 mg + metronidazole 125 mg + tetracycline HCl 125 mg, 3 capsules given four times a day	omeprazole 20 mg twice a day	10	The daily dosing pack is designed to hold: -12 3-in-1 capsules of Pylera each containing: 140 mg bismuth subcitrate potassium, 125 mg metronidazole in outer capsule and 125 mg tetracycline HCl in inner capsule -two omeprazole 20 mg capsules
esomeprazole (Nexium™)	esomeprazole 40 mg daily	clarithromycin 500 mg + amoxicillin 1,000 mg, each given twice a day	10	20 mg, 40 mg delayed-release capsule 20 mg, 40 mg delayed-release powder for oral suspension
lansoprazole (Prevacid®)	lansoprazole 30 mg twice a day	clarithromycin 500 mg + amoxicillin 1,000 mg, each given twice a day	10 to 14	15 mg, 30 mg delayed-release capsules 15 mg, 30 mg delayed-release orally disintegrating tablets
	lansoprazole 30 mg three times a day	amoxicillin 1,000 mg three times a day	14	
omeprazole (Prilosec®)	omeprazole 20 mg twice a day	clarithromycin 500 mg + amoxicillin 1,000 mg, each given twice a day	10 (14 days recommended by ACG)	10 mg, 20 mg, 40 mg delayed-release capsules 2.5 mg, 10 mg packets for oral suspension Continue with omeprazole 20 mg daily for 14 days in patients with active ulcer.
	omeprazole 40 mg daily	clarithromycin 500 mg three times a day	14	
rabeprazole (Aciphex®)	rabeprazole 20 mg twice a day	clarithromycin 500 mg + amoxicillin 1,000 mg, each given twice a day	7	20 mg delayed-release tablets

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Many of the trials with agents in this class were performed over a very short duration of treatment and in an open-label manner; introduction of bias must be considered when evaluating study findings.

lansoprazole, amoxicillin, and clarithromycin (Prevpac) for ten days versus 14 days

A multicenter, randomized, controlled, double-blind US trial with 236 patients evaluated the efficacy of triple therapy (lansoprazole 30 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg) given twice daily for ten days versus 14 days in the eradication of *H. pylori*.⁴⁸ There was no statistical difference in efficacy between the ten-day group (84 percent eradication) and the 14-day group (85 percent eradication). Adverse effects between the groups were similar.

A randomized, multicenter, prospective trial compared triple combination therapy (omeprazole 20 mg or an equivalent dose of a PPI, amoxicillin 1,000 mg and clarithromycin 1,000 mg) for seven days versus 14 days.⁴⁹ A total of 598 patients were enrolled (n=337 with seven day treatment and n=261 with 14 day treatment). The seven-day treatment was not inferior to the 14-day treatment (83.6 percent for seven day therapy and 86.6 percent for 14 day therapy). Adverse events were comparable in both groups.

bismuth, metronidazole, tetracycline (Pylera) with omeprazole versus triple therapy

In an open-label, multicenter, parallel group, active-controlled trial, the quadruple therapy of bismuth subcitrate potassium 1,680 mg daily, metronidazole 1,500 mg daily, and tetracycline 1,500 mg daily (Pylera) with omeprazole 20 mg twice daily had similar efficacy as the active control triple therapy of clarithromycin 500 mg daily, amoxicillin 1,000 mg daily and omeprazole 20 mg twice daily in the treatment of *H. pylori*-positive adults with current duodenal ulcer or a history of duodenal ulcer disease.⁵⁰ Eradication rates were 87.7 percent for quadruple therapy and 83.2 percent for the active control triple therapy. Gastrointestinal adverse events were similar for both arms.

Comparative Efficacy (for FDA-approved regimens)

Drug	Duration (days)	Eradication Rates (%)
Helidac ⁵¹	14	77 - 82*
Prevpac ^{52,53,54}	10 or 14	80 - 95.2
Pylera ⁵⁵	10	87.7
esomeprazole (Nexium) ⁵⁶	10	84 - 85
lansoprazole (Prevacid) ^{57,58,59}	10 to 14	80 - 95.2
	14	77
omeprazole (Prilosec) ^{60,61,62,63}	10 (14 days recommended by ACG)	69 - 90
	14	77 - 95
rabeprazole (Aciphex) ⁶⁴	7	77.3 - 84.3

*An unapproved regimen similar to Helidac using omeprazole 20 mg twice daily rather than an H₂-receptor antagonist had an eradication rate of 90 to 99 percent.⁶⁵

Meta Analyses

A meta-analysis evaluated randomized clinical trials comparing PPIs to H₂-antagonists with the same antibiotics.⁶⁶ Twenty studies fulfilled the inclusion criteria. In the intention-to-treat analysis, the mean eradication rates with PPIs and H₂-antagonists plus antibiotics were 74 and 69 percent, respectively. The analysis concluded that overall, PPIs were more effective than H₂-antagonists when prescribed at usual doses with antibiotics to eradicate *H. pylori* infection.

Triple therapy (PPI, clarithromycin, and amoxicillin or an imidazole) is the first-line treatment for *H. pylori* infection.⁶⁷ Quadruple therapy (PPI, tetracycline, metronidazole, and a bismuth salt) is a very effective regimen even in areas of high prevalence of antibiotic resistance. To compare triple versus quadruple therapy for the first-line treatment of *H. pylori* infection, an extensive literature search identified randomized trials comparing triple versus quadruple therapy. Four studies met the inclusion criteria. Eradication rates with quadruple therapy were slightly higher for both the intention-to-treat (81 versus 78 percent) and the per protocol analyses (88 versus 85 percent). The differences were not statistically significant.

A systematic evaluation as to whether sequential treatment eradicates *H. pylori* infection better than standard triple therapies and compare the risk of adverse events with these two regimens was conducted.⁶⁸ A comparison of studies evaluating the efficacy of the 10-day sequential therapy versus standard triple regimens for eradication of *H. pylori*, and the pooled risk ratios

(RR) and 95% confidence intervals (95% CI) were calculated for 11 randomized trials. Pooled analyses demonstrated clear superiority of the sequential therapy over seven-day triple regimen with an RR of 1.23 (95% CI, 1.19-1.27), and over 10-day triple regimen with a RR of 1.16 (95% CI, 1.10-1.23). Adverse event rates were similar for sequential therapy versus seven-day triple therapies, RR of 0.96 (95% CI, 0.70-1.31). In conclusion, sequential therapy was associated with a higher eradication rate of *H. pylori* compared with both seven-day triple regimen and ten-day triple regimen.

Summary

Triple and quadruple drug regimens are more effective at eradicating *H. pylori* than dual drug regimens. The most effective FDA-approved regimens are those that combine a PPI with amoxicillin and clarithromycin. This is likely due to the highly effective acid suppression provided by the PPI (in comparison to an H₂-antagonist) and the low rate of resistance to the two antibiotics (in comparison to metronidazole). These factors may reduce the usefulness of the combination product Helidac because of the required concomitant use of an H₂-antagonist.

The other triple combination product, Prevpac, combines the most effective components of triple therapy including a PPI. Prevpac is intended as a 14-day course of therapy. The newer combination therapy, Pylera along with omeprazole, offers quadruple drug therapy with competitive eradication rates compared to other triple drug regimens. Pylera may have a place in therapy for those patients who are allergic to amoxicillin or clarithromycin or in who bacterial resistance is known or suspected. Prevpac may be better suited for special populations such as pediatrics, pregnancy, and hepatic and/or renal insufficiency.

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