Use of newer combination products in the treatment of *H.pylori* infections: VPE/MAP Clinical Recommendations

November 2024

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised, as new clinical evidence is available. The purpose of this document is to assist practitioners in clinical decision-making and to standardize and improve the quality of patient care. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient.
The Product Information should be consulted for detailed prescribing information. The VA National PBM-MAP-VPE Cabotegravir Drug Monograph, Cabotegravir Criteria for Use & Descovy Criteria for Use are available at www.pbm.va.gov.

Background:

Helicobacter pylori (H. pylori) is one of the most common chronic infections in the world and a leading cause of infection related cancer, accounting for 80-90% of all gastric cancers. As a result, the World Health Organization (WHO) considers persistent *H.pylori* infection as a major threat to public health.

Resistance in *H.pylori* to macrolides and fluoroquinolones has increased substantially. A recent systematic review of over 2500 isolates of *H.pylori* from the United States found that 32% of isolates were clarithromycin resistant, and 38% levofloxacin resistant. Resistance to macrolides and fluoroquinolones markedly reduces effectiveness of triple regimens. While metronidazole resistance was also high (42%), it has less impact on the success of treatment regimens such as bismuth quadruple therapy.

Clarithromycin triple therapy (PPI + clarithromycin + amoxicillin) is no longer recommended as an empiric treatment option in treatment naïve patients.

American College of Gastroenterology 2024 Guidelines: Recommendations and Key Concepts:

- All patients found to be positive for *H.pylori* should be treated to reduce the risk of complications, including gastric cancer. All patients should undergo testing to ensure eradication after completion of a treatment regimen for *H.pylori.*
- **Treatment naïve patients**
  - Optimized bismuth quadruple therapy for 14 days is RECOMMENDED as a first line treatment option (strong recommendation, moderate quality of evidence)
    - Optimized bismuth quadruple therapy contains a bismuth salt, a nitroimidazole (at least 1.5 – 2 grams of metronidazole or tinidazole), tetracycline (preferred over doxycycline) and an appropriately dosed PPI.
  - Vonoprazan dual (VD) or rifabutin triple (TALICIA) 14 day regimens are SUGGESTED as first-line alternative treatment options (moderate quality evidence for VD, low quality for rifabutin triple).
- **Treatment-experienced patients**
  - Optimized bismuth quadruple therapy is suggested in those who have not previously received bismuth quadruple therapy
  - Rifabutin triple therapy is the only other suggested regimen in treatment-experienced patients that does not require susceptibility testing prior to use
  - Vonoprazan + amoxicillin + clarithromycin is suggested as a treatment option in treatment-experienced patients with known clarithromycin susceptible isolates
  - Levofloxacin triple therapy is suggested as a treatment option in treatment-experienced patients with known levofloxacin susceptible isolates

VHA VANF Clinical Recommendations:

TREATMENT NAÏVE PATIENTS

Optimized Bismuth Quadruple therapy: bismuth subsalicyclate 2 tablets QID + metronidazole 500mg TID - QID + tetracycline (not doxycycline) 500mg QID +PPI (at least BID or double-dose daily, 30-60 minutes before meals)

Optimized bismuth quadruple therapy is THE recommended first-line treatment option for patients with *H.pylori* infection who have not previously received it unless that regimen is contraindicated or cannot be used.

- Every effort should be made to optimize adherence to bismuth quadruple therapy
- Patients should be educated about the importance of completing all therapy as assigned and be educated about common side effects associated with bismuth quadruple therapy and that they rarely require discontinuation of the regimen.
- Optimized bismuth quadruple therapy is the ONLY treatment regimen that can be given to patients with a documented penicillin allergy. If this regimen cannot be used, patients should be referred to an allergist.

Vonoprazan + amoxicillin (VOQUEZNA DUAL PAK)

Vonoprazan + amoxicillin is suggested as an alternative in treatment-naïve patients when bismuth quadruple therapy cannot be used.

- Allergy to metronidazole or tetracycline, pregnancy, or other contraindications to bismuth quadruple therapy are possible reasons for use of VD in place of bismuth quadruple therapy.
- Amoxicillin resistance in the United States remains low, only 3% of patients in a recent systematic review.
- Vonoprazan + amoxicillin cannot be used in patients with true penicillin allergy.
- There are no significant data for use of VD in treatment-experienced patients and given the reliance on a single antibiotic, it should generally be reserved for treatment naïve patients who cannot use bismuth quadruple therapy.
- VOQUEZNA DUAL PAK is on the VA formulary as PA-F. See VHA Vonoprazan + amoxicillin (VOQUEZNA DUAL PAK) Monograph and Criteria for Use, for more information.

Rifabutin triple therapy (TALICIA or individual components)

- TALICIA (TAL) has been studied in treatment-naïve patients but not against a recommended standard treatment.
- Rifabutin triple-therapy can also be given to treatment-experienced patients without the need for susceptibility testing. This is the only other regimen besides optimized bismuth quadruple therapy that can be given without the need for susceptibility testing. This supports an argument to use rifabutin triple therapy or TALICIA when optimized bismuth quadruple and VD cannot be used or have failed.
- While TALICIA as a combination product has not been studied in treatment-experienced patients, the 2024 ACG guidelines suggest it as an alternative to the individual components in order to potentially maximize pharmacokinetics and potentially lower the risk of myelotoxicity.

TREATMENT-EXPERIENCED PATIENTS

Optimized bismuth quadruple therapy

Optimized bismuth quadruple therapy is the recommended treatment regimen for treatment-experienced patients who were not treated with bismuth quadruple therapy previously.

- Optimized bismuth quadruple therapy may also be an option for patients previously treated with less than optimal bismuth quadruple therapy if factors leading to failure can be addressed (such as compliance or discontinuation).
- A combination product that contains capsules which contain bismuth subcitrate 140mg, metronidazole 125mg and tetracycline 125mg (PYLERA) taken as 3 capsules 4 times daily (after meals and at bedtime), given in combination with a proton-pump inhibitor may simplify therapy for patients with difficulty

understanding and complying with traditional bismuth quadruple therapy, although it still contains a total pill burden of 14 capsules/tablets daily.

- PYLERA is packaged as a 10 day supply (10 blister packed cards) and when taken as directed may have doses of metronidazole (1.5g/day) and tetracycline (1.5g/day) lower than maximum recommended bismuth quadruple therapy.

Rifabutin triple therapy (TALICIA)

Rifabutin triple therapy is suggested in VHA for patients who have persistent *H.pylori* despite treatment with optimized bismuth quadruple therapy or VD.

- There is a substantial body of data with rifabutin triple therapy, given as individual components for salvage, including in patients with multiple treatment failures and the 2024 ACG guidelines suggest rifabutin triple therapy in persistent *H.pylori*.
  - While regimens vary, double dose PPI (or standard dose BID) + rifabutin 150mg BID or 300mg QD + amoxicillin 1000mg BID or TID is reasonable, with a pill burden of 8-10 tablet/capsules per day.
  - Rifabutin is a known CYP3A4 substrate and inducer and omeprazole inhibits CPY2C19, and patients should be evaluated for drug-drug interactions prior to prescribing rifabutin triple therapy (e.g. azole antifungals, antiretrovirals, warfarin, methotrexate, cyclosporine, tacrolimus).
  - As noted above, the proprietary product TALICIA (omeprazole, rifabutin and amoxicillin co-formulated in a delayed release capsule) was studied in treatment-naïve patients and is a suggested treatment alternative in the 2024 ACG *H.pylori* guidelines. Given as 4 capsules TID with food, it provides a totally daily dose of 120mg omeprazole, 150mg rifabutin and 2-3 g/day of amoxicillin, in a delayed release capsule that may have a pharmacokinetic advantage, resulting in intragastric rifabutin concentrations above the MIC_{90} of *H.pylori* for a longer period of time than 150mg BID or 300mg daily, acknowledging that TALICIA has not been studied in treatment-experienced patients.
- TALICIA is on the VA Formulary as PA-F. See VHA Criteria for Use, for more information.

Vonoprazan + clarithromycin + amoxicillin (VOQUEZNA TRIPLE PAK)

Vonoprazan triple therapy is suggested as a third-line treatment option if there are no contraindications AND the isolate has documented susceptibility to clarithromycin.

- Vonoprazan triple therapy was found in the primary Phase 3 trial to be noninferior to clarithromycin triple therapy and VD in treatment-naïve patients with clarithromycin-susceptible *H.pylori*.
- Both vonoprazan regimens were superior to clarithromycin-triple therapy (with a PPI) in all-treated patients and in those with clarithromycin-resistant isolates.
- Vonoprazan triple offered no benefit over vonoprazan dual therapy, which is why this regimen is not suggested as a first-line treatment regimen.
- In addition, clarithromycin adds gastrointestinal side effects, dysgeusia, and the potential for drug-drug interactions and QT prolongation.
- VOQUEZNA TRIPLE PAK is not on the VANF. See VHA vonoprazan + clarithromycin + amoxicillin Criteria for Use for more information

Levofloxacin triple therapy is also suggested as a third-line treatment option if there are no contraindications AND the isolate has documented susceptibility to levofloxacin

VA Formulary & Related Documents: PBM Home

- Vonoprazan + amoxicillin (Voquezna Dual Pak)) and vonoprazan + amoxicillin + clarithromycin (Voquezna Triple pak) Monograph
- Vonoprazan Dual Pak and Triple Pak Criteria for Use
- Rifabutin + amoxicillin + omeprazole Criteria for Use

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Prepared October 2024.

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APPENDIX 1: H.pylori Suggested Treatment Algorithm