Amoxicillin, Clarithromycin, Vonoprazan Fumarate (VOQUEZNA TRIPLE PAK®)
Amoxicillin, Vonoprazan Fumarate (VOQUEZNA DUAL PAK®)

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

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates may be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- VOQUENZA Triple Pak is a co-packaged product containing vonoprazan (VON), amoxicillin, and clarithromycin. Voquezna Dual Pak is a co-packaged product containing VON and amoxicillin. Both products were approved by the United States Food and Drug Administration (FDA) on 05/03/2022 for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults but were not marketed until approval of VON as a single agent for gastroesophageal reflux in November 2023. The FDA granted fast track status to VON co-packaged with antibiotics for the treatment of H. pylori infection in 2019. The individual VON product was approved for erosive esophagitis (EE) in November 2023.
- VON is a first-in-class potassium-competitive acid blocker (PCAB). In contrast to proton pump inhibitors, VON binds ionically (reversibly) rather than covalently, binds to active and inactive pumps (can be taken without regard to meals), does not require activation to an active moiety by acid, is acid stable, has a faster onset of acid suppressive effects (one dose vs 3–5 days), has a longer duration of action, and is not subject to variable effects due to CYP2C19 polymorphisms.

Indication(s) Under Review in This Document

- Treatment of *H. pylori* infection in adults

Dosage Form(s) Under Review and Dose

- VOQUENZA Triple Pak: VON 20 mg tablets with amoxicillin (AMOX) 1,000 mg and clarithromycin (CLARI) 500 mg in a prepackaged blister card to be taken 12 hours apart, with or without food.
    - In the morning: 1 tablet VON, 2 capsules of AMOX and 1 tablet CLARI
    - In the evening: 1 tablet VON, 2 capsules of AMOX and 1 tablet CLARI
- VOQUENZA Dual Pak: VON 20 mg BID plus amoxicillin 1,000 mg in a prepackaged blister card
    - In the morning: 1 tablet VON, 2 capsules AMOX
    - Mid-day: 2 capsules AMOX
    - In the evening: 1 tablet VON, 2 capsules AMOX

Clinical Evidence Summary

Efficacy Considerations

- The FDA reviewed data from 2 trials for approval.
  - HP-301, was the primary Phase 3 trial, and compared VON dual therapy (VD), VON triple therapy (VT) and lansoprazole triple therapy (LT) each for 14 days in the U.S. and Europe.
    - VD = VON 20mg BID + amoxicillin (amox) 1g TID
    - VT = VON 20mg BID + amox 1g BID + clarithromycin (clari) 500mg BID
    - LT = lansoprazole (lansop) 30mg BID + amox 1g BID + clarithromycin (clari) 500mg BID
  - CCT-401 was a randomized, blinded trial conducted in Japan which compared VT vs. LT, each for 7 days.
    - VT = VON 20mg BID + amox 750mg BID + clari 200 or 400mg BID
    - LT = Lansop 30mg BID + amox 750mg BID + clari 200 or 400mg BID
  - Several meta-analyses including other randomized and nonrandomized studies provide additional supportive evidence.

Table 1: Efficacy of VON dual (VD) and VON triple therapy (VT) from clinical trials

Study	Methods	Population	Results
HP-301 Study – Phase 3 Chey et al. Multicenter, randomized, double-blind trial comparing VD and VT to LT. Conducted in U.S. and Europe	**Interventions** (1:1:1 randomization) -VD (open-label): n=349 -VT: (double-blind): n=349 -LT: (double-blind): n=348 **Key Inclusion Criteria** Symptomatic *H. pylori* infection confirmed by C-urea breath test (*dyspepsia, recent/new diagnosis of non-bleeding peptic ulcer, history of peptic ulcer not previously treated for H. Pylori)* **Key Exclusion Criteria** Prior treatment for H. pylori; gastric cancer, current/recent bleeding ulcer, lupus erythematosus, Zollinger-Ellison syndrome, SCr >2 mg/dL, ALT, AST or total bilirubin >2x ULN **Primary outcome:** % eradication *H.pylori* by C-urea breath test (C-UBT) 4 weeks after the last dose in patients without amox or clari resistance at baseline in full analysis set (FAS) **Secondary outcomes:** % eradication by C-UBT at 4 weeks in those WITH clarithromycin resistance at baseline % eradication by C-UBT at 4 weeks in all patients	Mean age 51-52 years 35-40% male 90% white 41-43% U.S. participants **Primary condition dyspepsia**, % • VD: 96% • VT: 99% • LT: 99% **Clari resistance, %** • **VD: 19%** • **VT: 24%** • **LT: 24%** Amox resistance, % • VD: 1% • VT: 2% • LT: 1% Metro resistance, % • VD: 67% • VT: 70% • LT: 71%	**Primary Outcome** Eradication in subjects **WITHOUT** clari resistance at baseline in FAS • VD **79%** • VT **85%** • LT **79**% VD vs. LT diff. -0.3%, 95%CI (-7, 7) VT vs. LT diff. 6%, 95% CI (-1, 13) **Noninferiority met both VD/VT** **Secondary Efficacy Endpoints** Eradication in subjects **WITH** clari resistance at baseline in FAS • VD 70% (95% CI, 20.5–52.6) • VT 66% (95% CI, 17.7–48.1) • LT 32% VD vs. LT diff. 38% (95%CI 21, 53) VT vs. LT diff. 34% (95%CI 18, 48) P<0.001 for both **VD/VT superior to LT in subjects with baseline clari resistance** Eradication in all subjects in FAS • VD 77% • VT 81% • LT 69% VD vs. LT diff. 12% (95% CI 2,15) VT vs. LT diff. 9% (95%CI, 6, 19) P<0.001 and p=0.013 **VD/VT superior to LT in ALL**
CCT-401 Study - Phase 3	**Interventions** • VT: n=329 (168 clari 200mg, 161 clari 400mg) • LT: n=321 (164 clari 200mg, 157 clari 400mg)	Mean age, 55 and 54 yrs. 60% male	**Primary Endpoint:** 4wk. eradication • VT 93% • LT 76%

Murakami, 2016 Multicenter, randomized, double-blind trial comparing VT to LT. Conducted in Japan	• Open-label VT option (VON+amox+metro) if failed in either treatment group; n=50 **Key Inclusion Criteria** • *H pylori*+ patients aged ≥20 years **with gastric (GU) or duodenal ulcer (DU) history** • H pylori confirmed via rapid urease, culture, C-UBT, and/or stool H pylori antigen **Key Exclusion Criteria** • Acute upper GI bleeding, active or acute GU or DU, prior *H. pylori* therapy, Zollinger–Ellison syndrome, upper GI surgery **Primary endpoint:** eradication by C-UBT 4 weeks after last dose in FAS (all randomized who received at least 1 dose) **Secondary endpoint:** 2nd line eradication in those who failed first line treatment **Post-hoc analyses, eradication in specific subgroups** (no adjustment for multiplicity)	Amox resistance, % • VT: 22% • LT: 23% **Clari resistance, %** • **VT: 30%** • **LT: 36%** Metro resistance, % • VT: 8% • LT: 8% CYP2C19 % extensive metabolizers: • VT: 83% • LT: 85%	**Diff 17% (95% CI; 11, 22), p<0.0001 noninferiority margin met and VT superior to LT** **Secondary Endpoint,** 4 wk. eradication after open-label VT for failed first-line therapy • Second-line VT w/ MTD 98% **Post-hoc analyses: subgroups (VT vs. LT)** • Age≥65: 91% vs. 82% (p=NS) • **Clari-R: 82% vs. 40% (p<0.001)** • Amox MIC>0.03: 87% vs. 59% (p=0.0003) • **Clari 200: 93% vs. 79% (p=0.003)** • **Clari 400: 92% vs. 73% (p<0.0001)** • **CYP2C19 EM: 93% vs. 75% (p<0.0001)**

VD = VON dual; VT = VON triple; LT = lansoprazole triple; MTD = metronidazole

Efficacy Summary

- Data from the large Phase 3 trial of VD and VT demonstrated both regimens were non-inferior to standard triple therapy with a PPI

Safety Considerations

Study	Results

HP-301 **Study – Phase 3**	• Treatment discontinuation due to adverse events (AEs) in 2.3% VT, 0.9% VD and 1.2% LT
	• Overall adverse events similar
	• Most Common TEAEs (occurred in >4% patients)
	  ○ Diarrhea: 5% VD vs. 4% VT vs. 10% LT
	  ○ Dysgeusia: 1% VD, 5% VT vs. 6% LT
	  ○ Vulvovaginal candidiasis: 2% VD vs. 3% VT vs. 1% LT
	• Three deaths: 2 COVID-19 (1 patient each on LT and VT), and 1 fatal, sudden cardiac arrest (patient on VT).

CCT-401 **Study – Phase 3 from Japan**	• The incidence of TEAEs, drug-related TEAEs, TEAEs leading to study drug discontinuation and serious TEAEs were comparable between the treatment groups.
	• No significant changes were observed in mean laboratory test values, vital signs or electrocardiogram findings during the study.
	• Most Common TEAEs (occurred in >2% patients)
	  ○ Diarrhea: 13% VT v. 15% LT
	  ○ Nasopharyngitis: 6% VT vs. 5% LT
	  ○ Dysgeusia: 4% VT vs. 3% LT

VD = VON dual; VT = VON triple; LT = lansoprazole triple

- **Contraindications:**
  - Hypersensitivity to any component (including hypersensitivity to drugs in the same class)

- Contraindication to clari, including contraindicated concomitant medications or a history of cholestatic jaundice / hepatic dysfunction with prior clari.
- Concomitant use with rilpivirine-containing products

- **Other warnings / precautions**:
  - **Hypersensitivity reactions** – serious and fatal reactions have been reported with components.
  - **Acute tubulointerstitial nephritis** – has been reported with VON.
  - **Severe cutaneous adverse reactions (**e.g., Stevens-Johnsons syndrome / toxic epidermal necrolysis)
  - **Drug induced enterocolitis syndrome** – reported with amoxicillin, most commonly in pediatric patients, presenting as protracted vomiting 1-4 hours after drug-injection.
  - ***Clostridioides difficile* associated diarrhea**
  - **Rash with mononucleosis** – due to amoxicillin component
  - **Interaction with diagnostic investigations for neuroendocrine tumors** – can cause false positive results in diagnostic investigations for neuroendocrine tumors secondary to drug-induced decreases in gastric acidity
  - **Development of resistant bacteria**
  - **Additional warnings due to clarithromycin in VOQUENZA Triple Pak only**
    - **QT prolongation** – avoid: known prolonged QT, ventricular arrhythmia or other drugs / conditions known to prolong the QT interval
    - **Hepatotoxicity** – clari can cause hepatocellular and/or cholestatic hepatitis
    - **Drug interactions** – serious adverse events have been reported with clari when given concomitantly with drugs metabolized by CYP3A4. See prescribing information for details.
    - **Embryofetal toxicity** – clari demonstrated adverse effects on pregnancy outcomes, including increased risk of miscarriage and in some studies an increased risk of fetal malformations. Studies in animals produced cleft palate and cardiovascular abnormalities at clinically relevant doses, as well as reduced fetal survival, body weight and weight gain.
      - **VOQUEZNA Triple Pak is NOT recommended in pregnancy unless no alternative therapy is appropriate**.
    - **Infertility:** Based on animal fertility study findings for clarithromycin, VT may impair fertility in males of reproductive potential.
    - **Exacerbation of myasthenia gravis**

- **Adverse reactions (AE)**
  - Safety databased for VT = 675 adults (U.S., Europe and Japan) and for VD = 348 adults (U.S. and Europe)
    - Most common relevant AE (≥ 2% - VD vs. VT vs. LT)
      - Diarrhea (5% vs. 4% vs. 10%)
      - Dysgeusia (1% vs. 5% vs. 6%)
      - Vulvovaginal candidiasis (2% vs. 3% vs. 1%)
      - Abdominal pain (3% vs. 2% vs. 3%)
      - Headache (1% vs. 3% vs. 1%)
    - AEs leading to discontinuation
      - VD: 1%
      - VT: 2%
      - LT: 1%
  - Other post-marketing AEs with VON (alone):
    - Thrombocytopenia
    - Anaphylactic shock, urticaria, drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
    - Hepatic injury, hepatic failure, jaundice

- **Systematic review and meta-analysis: Randomized trials of VD vs. bismuth quadruple therapy (BisQ)**
  - Evaluated 6 RCTs, all in Asia (n=1233)
  - ***H.pylori* eradication (ITT):**
    - VD 87%
    - BisQ 86%

  Total adverse events

  VD 16%

  BisQ 40%: RR 0.45, 95% CI (0.37, 0.55) Less nausea/vomiting and taste disorder
- **Systematic review and meta-analysis: Randomized and non-randomized, all in China (9 RCT, 1 NR, n=2587)**
  - Variety of VON containing regimens compared against Bismuth containing regimens
  - ***H.pylori* eradication ITT (9 studies):**
    - VON 90%
    - PPI-BisQ 84% **OR 1.9, 95% CI (1.3, 2.7) p=0.001**
  - **Total adverse events**
    - **VON 15%**
    - **BisQ 26% OR 0.49, 95% CI (0.32, 0.75)**

Other Considerations

- **Pharmacokinetics (VON only)**:
  - **Absorption**
    - Onset of antisecretory effect occurs within 2-3 hours of a 20mg dose
    - Drugs requiring acid for absorption may have reduced AUC with VON (e.g. rilpivirine)
  - **Distribution**
    - Plasma protein binding 85 to 88%
  - **Metabolism**
    - Multiple metabolic pathways, including **CYP3A4/5**, CYP2B6, CYP2C19, and CYP2D6 along with sulfo- and glucuronosyl-transferases. CYP2C19 polymorphisms do not impact VON PK
  - **Excretion**
    - 67% in urine (8% unchanged), 31% in feces (1.4% unchanged)
  - **Pk Drug Interactions**
    - VON inhibits CYP2B6, CYP2C19, and CYP3A4/5
      - Increases in drugs metabolized by these enzymes
    - Clarithromycin (CYP3A inhibitor) increased VON AUC 58% versus VON alone
    - VON exposures are predicted 80% lower with strong CYP3A4 inducers (e.g. rifampicin) and 50% lower with a moderate CYP3A4 inducer (e.g. efavirenz).

- **Special populations**:
  - **Pregnancy**: No adequate and well-controlled studies of VON in pregnant women to evaluate for drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Studies in rats and rabbits did show possible harm (liver discoloration with necrosis in rats born to mothers who received VON during pregnancy and lactation). Clari is associated with increased of miscarriage and possible major congenital malformations.
  - **Renal impairment**: No dose adjustment needed for estimated GFR ≥ 30 mL/min. Not recommended with GFR < 30 mL/min.
  - **Hepatic impairment**: Standard doses for patients with Child-Pugh A hepatic impairment. Not recommended in Child-Pugh B or C.

Treatment naïve patients	# pills per day / Duration	Advantages	Other considerations
Voquezna dual pak VON BID + Amox 1g TID	8 pills/d 14 days	Packaged together Higher amoxicillin dose Lowest pill burden Suggested first-line regimen in guidelines May have lower adverse events than bismuth quadruple	Three times daily dosing Significantly more expensive than bismuth quadruple and is suggested (rather than recommended) given the higher level of evidence with bismuth quadruple. May be useful in patients who cannot use bismuth quadruple (e.g. allergy to metronidazole or tetracycline or PPI)
Optimized Bismuth Quad PPI BID + bismuth subsalicylate QID + tetracycline 500mg QID + metro QID	14 pills/day 14 days	First line in updated ACG Guidelines Only regimen that can be used in patients with true penicillin allergy	High pill burden Adverse events very common (GI, taste disturbance, black stool) but rarely lead to discontinuation
Rifabutin triple therapy PPI BID + Rifabutin 300mg QD + Amoxicillin 1g BID-TID **Rifabutin triple – commercial: Talicia** combination tablet of amoxicillin / omeprazole and rifabutin given as 4 capsules TID with food	8-10 pills/d 14 days 12 pills/d 14 days	Low rates of resistance Can be used as salvage, making it perhaps more valuable for that population Commercial delayed release capsule may optimize PK/PD and reduce confusion	Drug-drug interactions. Using individual components may not achieve optimal gastric concentrations for rifabutin Talicia more expensive than using individual components but may improve compliance and reduce copays
Salvage Regimens / Treatment-experienced			
Voquezna triple pak VON BID + amox 1g BID + clari 500mg BID	8 pills/d 14 days	All packaged together Twice daily dosing	Adverse events and contraindications due to clarithromycin, drug-drug interactions Requires susceptibility to clarithromycin be demonstrated
Optimized Bismuth quad as above ***Pylera*** *(combo bismuth subcitrate, metro, tetracycline) 3 caps QID + PPI BID*	8 pills/d 14 days	See above	See above – may be effective even if previously used but not optimized or discontinued due to compliance – use of combination product may be of benefit in this situation
Rifabutin triple PPI (standard or double dose), Amox 1g BID or TID, Rifabutin 50-300mg (or Talicia)	7-14 pills/d 14 days	May assist if clari resistance by addition of bismuth and tetracycline	See above
PPI triple therapy (PPI + clari + amoxicillin)			NO LONGER RECOMMENDED – if Triple therapy with a macrolide, guidelines prefer vonoprazan based triple therapy
High-dose dual Double-dose PPI BID + amoxicillin 1g TID or 750mg QID	10-14 pills/d 14 days	? efficacy Maybe people who cannot tolerate other	NO LONGER RECOMMENDED- may be select circumstances where this regimen could be used but vonoprazan dual therapy preferred.

Projected Place in Therapy

- *Helicobacter pylori* is a common chronic infection with a prevalence of up to 40% in North America.
    - Dyspepsia, peptic ulcer disease, gastric adenocarcinoma and marginal zone B-cell lymphoma (MALToma) are long term sequelae of chronic *H.pylori* infection.
    - All patients positive for *H.pylori* treatment should be offered treatment **with a test of cure after treatment** to reduce the risk of complications associated with infection including gastric cancer.
    - In a cohort of Veterans from 1999-2018, the prevalence of *H.pylori* infection ranged from 12%-30%, with highest rates seen in Hispanic (24%) and non-Hispanic black (30%) patients, compared to 12% in non-Hispanic white individuals. Of note, *H.pylori* positivity decreased from 36% in 1999-2006 to 18% in 2013-2018.

- Published in 2024, the updated American College of Gastroenterology (ACG) guidelines have removed PPI-based triple therapy with clarithromycin or levofloxacin containing regimens in the absence of susceptibility testing, based on a US survey that identified resistance rates of 32% for clari and 38% for levofloxacin, as well as 43% resistance for metronidazole. Resistance to tetracycline, amoxicillin and rifabutin were < 3%.
    - Resistance to macrolides or fluoroquinolones markedly decreases efficacy of PPI based triple therapy while resistance to metronidazole does not have a significant impact on efficacy of bismuth quadruple therapy
- **Optimized bismuth quadruple therapy (BQT) for 14 days is the only recommended first-line treatment option**.
    - BQT is complex and associated with a high rate of adverse events, but rarely leads to discontinuation and can be used in penicillin-allergic patients.
    - Guidelines prefer tetracycline over doxy based on a single study where effectiveness was 70% with doxy in BQT, versus 87% with tetracycline, although the number of patients on doxy was small, and acquisition of tetracycline has sometimes been problematic in recent years.
    - A generic combination product (similar to Pylera) contains the ingredients in the regimen but is more expensive than using the individual components and offers little advantage over giving the individual components other than ease of dosing from a single prescription. This may be useful for patients who failed BQT due to confusion or compliance with individual components.
- **Voquezna-amoxicillin dual pak is a suggested first-line option for the treatment of H. pylori in treatment-naïve patients** based on the results of HP-301, which showed noninferiority in subjects with clari-susceptible strains and superiority with clari-resistant strains as well as the full mITT population.
    - VD and VT were well-tolerated compared to LT, and meta-analyses have suggested VD is better tolerated than bismuth quad therapy
    - Outcomes of VD and VT were similar, which is why VD is a **suggested** first-line option, while VT is suggested as salvage, when clarithromycin susceptibility can be documented.
    - VD and VT can be given without regard to food and isn't impacted by genetic polymorphisms as some PPIs are.
- **Rifabutin-based triple therapy (PPI + rifabutin + amoxicillin) is also suggested as a first-line treatment**.
    - This combination is available as a proprietary combination regimen, with all drugs included in a single delayed-release capsule (TALICIA).
    - TALICIA is more expensive than combining the individual agents, but a pharmacokinetic study suggested the frequent dosing may maintain intragastric concentrations of rifabutin longer than 150mg or 300mg once or twice daily
- **Given differences in cost and the 2024 ACG guidelines, it is reasonable to consider bismuth based quadruple therapy first-line, with Voquezna dual reserved for those who cannot tolerate bismuth quadruple therapy.**
- **While rifabutin triple, as Talicia, is also a suggested first-line regimen, it may be more beneficial as a second-line empiric regimen in those who fail first-line therapy, especially if bismuth quadruple therapy cannot be used.**
- **Other regimens (e.g. Voquezna triple pak or levofloxacin based therapy) would require susceptibility testing which adds significant cost and complexity**

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