NEW DRUG APPROVAL

Brand Name	Voquezna™ Triple Pack™
Generic Name	amoxicillin; clarithromycin; vonoprazan fumarate
Drug Manufacturer	Phathom Pharmaceuticals, Inc.

New Drug Approval

FDA approval date: May 3, 2022

Review designation: Priority

Type of review: Type 1 - New Molecular Entity and Type 4 - New Combination; New Drug Application (NDA): 215152

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

H. pylori is a gram-negative, microaerophilic bacterium that can infect humans. It is often found in the stomach of affected individuals and causes inflammation and ulceration. Patients harboring the bacteria are asymptomatic with abdominal pain, nausea, vomiting, and dyspepsia developing only after gastritis and peptic ulcer disease. H. pylori is the most important cause for chronic or atrophic gastritis, peptic ulcer, gastric lymphoma, and gastric carcinoma. However, these complications are less often seen in children and adolescents compared to adults. H. pylori infection is usually acquired in early childhood and persists in the absence of treatment. Transmission of H. pylori can occur via the fecal-oral, gastric-oral, oral-oral, or sexual routes.

Prevalence of H. pylori varies across the world, with the United States having 5% prevalence in children less than 10 years. The Hispanic and African American populations have a higher prevalence compared to White Americans.

Efficacy

The effectiveness and safety of Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™ were evaluated in a randomized, controlled, double-blind triple therapy/open-label dual therapy study conducted in the United States and Europe in treatment-naïve H. pylori-positive adult patients with at least one clinical condition: dyspepsia lasting at least 2 weeks, functional dyspepsia, recent/new diagnosis of peptic ulcer, peptic ulcer not treated for H. pylori infection, or a stable dose of long-term NSAID treatment (NCT 04167670). Patients were randomized 1:1:1 to vonoprazan 20 mg twice daily plus amoxicillin 1,000 mg twice daily plus clarithromycin 500 mg twice daily (Voquezna™ Triple Pack™) or vonoprazan 20 mg twice daily plus amoxicillin 1,000 mg three times daily (Voquezna™ Dual Pack™) or lansoprazole 30 mg twice daily plus amoxicillin 1,000 mg twice daily plus clarithromycin 500 mg twice daily (LAC) administered for 14 consecutive days.

H. pylori infection at baseline was defined as positive by 13C urea breath test (UBT) and follow-up upper endoscopy (culture or histology). H. pylori eradication was confirmed with a negative 13C UBT test-of-cure at ≥ 27 days post-therapy. Patients with negative test results were considered treatment successes. Patients who tested positive for H. pylori infection and patients with missing results from the test-of-cure visit were considered treatment failures.

Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™ were shown to be noninferior to LAC in patients who did not have a clarithromycin or amoxicillin resistant strain of H. pylori at baseline. Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™ were shown to be superior to LAC in patients who had a clarithromycin resistant strain of H. pylori at baseline and in the overall population.

H. pylori eradication rates are shown in Table 1 for Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™ compared to LAC.

Table 1: Eradication Rates of H. pylori in Patients Receiving Voquezna™ Triple Pack™, Voquezna™ Dual Pack™, or LAC at ≥27 Days Post-therapy - mITT

	Voquezna™ Triple Pack™ % (n)	Voquezna™ Dual Pack™ % (n)	LAC % (n)
Patients with H. pylori infection who did not have a clarithromycin or amoxicillin resistant strain at baseline[a]	84.7 (222)	78.5 (208)	78.8 (201)
Treatment Difference from LAC (95% CI)	5.9[b] (-0.8, 12.6)	-0.3[c] (-7.4, 6.8)	
All randomized patients with H. pylori infection at baseline	80.8 (273)	77.2 (250)	68.5 (226)
Treatment Difference from LAC (95% CI)	12.3[d] (5.7, 18.8)	8.7[e] (1.9, 15.4)	
Patients with H. pylori infection who had a clarithromycin resistant strain of H. pylori at baseline	65.8 (48)	69.6 (39)	31.9 (23)
Treatment Difference from LAC (95% CI)	33.8[f] (17.7, 48.1)	37.7[f] (20.5, 52.6)	

LAC = lansoprazole, amoxicillin, clarithromycin triple therapy regimen; CI = confidence interval calculated via the Miettinen and Nurminen method.

Modified intent to treat (mITT) population: Patients were included in the MITT analysis if they had documented H. pylori infection at baseline.

[a]Clarithromycin resistant strains of H. pylori were considered those with an MIC ≥ 1 µg/mL; amoxicillin resistant strains were considered those with an MIC > 0.125 µg/mL.

[b]p< 0.01 for test of non-inferiority versus LAC.

[c]p< 0.01 for test of non-inferiority versus LAC.

[d]p=0.0003 for test of superiority versus LAC.

[e]p=0.01 for test of superiority versus LAC.

[f]p< 0.0001 for test of superiority versus LAC.

Safety

ADVERSE EVENTS

Treatment discontinuation due to an adverse reaction occurred in 2.3% (8/346) of the Voquezna™ Triple Pack™-treated patients, 0.9% (3/348) of the Voquezna™ Dual Pack™ -treated patients and 1.2% (4/345) of the LAC-treated patients. The most common adverse reactions leading to discontinuation of Voquezna™ Triple Pack™ were diarrhea (0.6%) and hypertension (0.6%) and the most common adverse reaction leading to discontinuation of Voquezna™ Dual Pack™ was rash (0.6%).

The adverse reactions occurring in ≥2% of patients are described in Table 2:

Table 2: Adverse Reactions Occurring in ≥2% of Adult Patients Receiving Voquezna™ Dual Pack™ or Voquezna™ Triple Pack™

Adverse Reactions	Voquezna™ Dual Pack™ (N=348) n (%)	Voquezna™ Triple Pack™ (N=346) n (%)	LAC (N=345) n (%)
Diarrhea	18 (5.2)	14 (4.0)	33 (9.6)
Dysgeusia[a]	2 (0.6)	16 (4.6)	21 (6.1)
Vulvovaginal candidiasis[b]	7 (2.0)	11 (3.2)	5 (1.4)
Abdominal pain[c]	9 (2.6)	8 (2.3)	10 (2.9)
Headache	5 (1.4)	9 (2.6)	5 (1.4)
Hypertension[d]	4 (1.1)	7 (2.0)	3 (0.9)
Nasopharyngitis	7 (2.0)	1 (0.3)	3 (0.9)

[a]Dysgeusia also includes taste disorder.

[b]Vulvovaginal candidiasis includes: urogenital infection fungal, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginal pruritus, pruritus genital, genital infection fungal.

[c]Abdominal pain includes: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper.

[d]Hypertension also includes blood pressure increased.

WARNINGS & PRECAUTIONS

Hypersensitivity Reactions- Serious and occasionally fatal hypersensitivity reactions (e.g., anaphylaxis, anaphylactic shock, rash, erythema multiforme, and Henoch-Schonlein purpura) have been reported with components of Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™. Before initiating therapy with Voquezna™ Triple Pack™ or Voquezna™ Dual Pack™ careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, macrolide antibacterial drugs or other allergens. Discontinue Voquezna™ Triple Pack™ Voquezna™ Dual Pack™ immediately and institute appropriate treatment if hypersensitivity occurs.

Severe Cutaneous Adverse Reactions- Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the components of Voquezna™ Triple Pack™: vonoprazan, amoxicillin and clarithromycin and Voquezna™ Dual Pack™: vonoprazan and amoxicillin. In addition, drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported with amoxicillin and clarithromycin. Discontinue Voquezna™ Triple Pack™ or Voquezna™ Dual Pack™ at the first signs or symptoms of SCAR or other signs of hypersensitivity and consider further evaluation.

Clostridioides difficile-Associated Diarrhea- Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of acid suppressing therapies and nearly all antibacterial agents, including amoxicillin (component of Voquezna™ Dual Pack™ and Voquezna™ Triple Pack™) and clarithromycin (component of Voquezna™ Triple Pack™), and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of Clostridioides difficile (C. difficile).

Rash in Patients with Mononucleosis- A high percentage of patients with mononucleosis who receive amoxicillin (a component of Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™) develop an erythematous skin rash. Avoid use of Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™ in patients with mononucleosis.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors - Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Assess CgA levels at least 14 days after Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™ treatment and consider repeating the test if initial CgA levels are high.

Development of Drug-Resistant Bacteria- Prescribing Voquezna™ Triple Pack™ or Voquezna™ Dual Pack™ in the absence of a proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

QT Prolongation- Clarithromycin (a component of Voquezna™ Triple Pack™) has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving clarithromycin. Fatalities have been reported. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Hepatotoxicity- Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin (a component of Voquezna™ Triple Pack™). This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Symptoms of hepatitis can include anorexia, jaundice, dark urine, pruritus, or tender abdomen. Discontinue Voquezna™ Triple Pack™ immediately if signs and symptoms of hepatitis occur.

Embryo-Fetal Toxicity with Use of Voquezna™ Triple Pack™- Based on findings from animal studies and human observational studies in pregnant women with use of clarithromycin, Voquezna™ Triple Pack™ is not recommended for use in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If Voquezna™ Triple Pack™ is used during pregnancy, or if pregnancy occurs while the patient is taking this drug, advise the patient of the potential risk to the fetus. Clarithromycin demonstrated adverse effects on pregnancy outcome and/or embryo fetal development, in pregnant animals administered oral clarithromycin. Observational studies in pregnant women also demonstrated adverse effects on pregnancy outcomes, including an increased risk of miscarriage and in some studies an increased incidence of fetal malformations.

Exacerbation of Myasthenia Gravis- Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic syndrome has been reported in patients receiving clarithromycin therapy (a component of Voquezna™ Triple Pack™). Monitor patients for symptoms.

CONTRAINDICATIONS

Hypersensitivity Reactions- Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™ are contraindicated in patients with a known hypersensitivity to any component of Voquezna™ Triple Pack™: vonoprazan, amoxicillin (or other βlactam antibacterials, e.g., penicillins and cephalosporins) or clarithromycin (or other macrolide antibacterial drugs, e.g., erythromycin) or Voquezna™ Dual Pack™: vonoprazan or amoxicillin (or other β-lactam antibacterials, e.g., penicillins and cephalosporins).

Rilpivirine-containing Products- Voquezna™ Triple Pack™ and Voquezna™ Dual Pack™ are contraindicated with rilpivirine-containing products.

Serious Adverse Reactions/Risks Due to Drug Interactions- Because of the clarithromycin component, Voquezna™ Triple Pack™ is contraindicated with concomitant use of:

- **Pimozide**: There have been postmarketing reports of drug interactions when clarithromycin is co-administered with pimozide, resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of metabolism of these drugs by clarithromycin. Fatalities have been reported.
- **Lipid-lowering Agents**: Lomitapide, simvastatin, and lovastatin.

- **Ergot Alkaloids**: Ergotamine or dihydroergotamine.
- **Colchicine**: Colchicine in patients with renal or hepatic impairment.

Cholestatic Jaundice/Hepatic Dysfunction- Voquezna™ Triple Pack™ is contraindicated in patients with a history of cholestatic jaundice or hepatic dysfunction associated with prior use of clarithromycin.

Clinical Pharmacology

MECHANISMS OF ACTION

Vonoprazan suppresses basal and stimulated gastric acid secretion at the secretory surface of the gastric parietal cell through inhibition of the H+, K+-ATPase enzyme system in a potassium competitive manner. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, vonoprazan has been characterized as a type of gastric proton-pump inhibitor, in that it blocks the final step of acid production. Vonoprazan does not require activation by acid. Vonoprazan may selectively concentrate in the parietal cells in both the resting and stimulated states. Vonoprazan binds to the active proton pumps in a noncovalent and reversible manner. Amoxicillin is an antibacterial drug. Clarithromycin is a macrolide antimicrobial drug. Acid suppression enhances the replication of H. pylori bacteria and the stability and effectiveness of antimicrobials in the treatment of H. pylori infection.

Dose & Administration

ADULTS

20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each given twice daily (in the morning and evening, 12 hours apart), with or without food, for 14 days.

PEDIATRICS

None

GERIATRICS

None

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Voquezna™ Triple Pack™: Carton of 14 daily administration packs for morning and evening dosing, each containing the following three drug products:

- Tablets: Vonoprazan 20 mg
- Tablets: Clarithromycin 500 mg
- Capsules: Amoxicillin 500 mg