PHARMACY COVERAGE GUIDELINE

VOQUEZNA® (vonoprazan)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Voquezna (vonoprazan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Healing of all grades of **erosive esophagitis** and relief of heartburn associated with erosive esophagitis

b. Maintain healing of all grades of **erosive esophagitis** and relief of heartburn associated with erosive esophagitis

c. Relief of heartburn associated with **non-erosive gastroesophageal reflux disease (NERD)**

d. Treatment of ***Helicobacter pylori* (*H. pylori*) infection** in combination with amoxicillin and clarithromycin **OR** in combination with amoxicillin alone

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. **For erosive esophagitis ALL** of the following**:**
      i. Endoscopic confirmation of erosive esophagitis
      ii. Los Angeles classification grade C or D (see Definitions section)
      iii. Heartburn symptoms two or more times per week
   b. **For non-erosive gastroesophageal reflux disease ALL** of the following:
      i. History of heartburn for 6-months or longer
      ii. Heartburn on at least 4 of 7 days
      iii. No esophageal erosions on endoscopy
      iv. Negative for *H. pylori* infection
   c. **For H. pylori**: a positive ^{13}C urea breath test (UBT) for *H. pylori* and **ONE** of the following:
      i. Dyspepsia for at least 2 weeks
      ii. Functional dyspepsia (i.e., dyspepsia from no known cause)
      iii. Recent or new diagnosis of non-bleeding peptic ulcer
      iv. History of peptic ulcer not previously treated for *H. pylori* infection
      v. Requires long-term non-steroidal anti-inflammatory drug treatment using a stable dose
   d. Serum magnesium and calcium levels

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** the following:
   a. **For erosive esophagitis/heartburn** – use of two times the standard doses of **TWO** of the following proton pump inhibitors (see Definitions section):
      i. Dexlansoprazole: 30 mg twice daily
      ii. Esomeprazole: 20 mg twice daily
      iii. Lansoprazole: 30 mg twice daily
      iv. Omeprazole: 20 mg twice daily
      v. Pantoprazole: 40 mg twice daily
      vi. Rabeprazole: 20 mg twice daily
   b. **For non-erosive gastroesophageal reflux disease heartburn** – use of standard doses of **TWO** of the following (see Definitions section):
      i. Dexlansoprazole: 30 mg once daily
      ii. Esomeprazole: 20 mg once daily
      iii. Lansoprazole: 30 mg once daily
      iv. Omeprazole: 20 mg once daily
      v. Pantoprazole: 40 mg once daily

vi. Rabeprazole: 20 mg once daily

c. **For H. pylori infection:**
   i. Patients **without** risk factors for macrolide resistance **ONE** of the following: (see Definitions section)
      1. A proton pump inhibitor (PPI), amoxicillin, and clarithromycin
      2. A proton pump inhibitor (PPI), metronidazole, and clarithromycin
   ii. Patients **with** risk factors for macrolide resistance (see Definitions section)
      1. A proton pump inhibitor (PPI), metronidazole, tetracycline and bismuth subsalicylate

7. Individual is not currently taking any other drugs which may result in a significant drug interaction requiring discontinuation such as:
   a. Concurrent use with atazanavir or nelfinavir
   b. Moderate or strong CYP3A4 inducers (see Definitions section)

8. Individual does **NOT** have the FDA-label contraindication of concurrent use with Rilpivirine-containing products

9. **For H. pylori infection only**: Requested agent **will not** be used if estimated GFR is less than 30 mL/min

10. **For H. pylori infection only**: Requested agent **will not** be used in moderate to severe hepatic impairment (Child-Pugh Class B and C)

Initial approval duration:
14 days: *H. pylori* infection
4 weeks: Relief of heartburn associated with non-erosive gastroesophageal reflux disease (NERD)
8 weeks: Healing of erosive esophagitis
6 months: Maintenance erosive esophagitis

- **Criteria for continuation of coverage (renewal request):** Voquezna (vonoprazan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist

2. Individual's condition has responded while on therapy with response defined as the following:
   a. **For erosive esophagitis healing:**
      i. Endoscopic evidence of complete healing
      ii. Increased number of days without heartburn
      iii. Maintains healing and resolution of heartburn symptoms
   b. **For non-erosive gastroesophageal reflux disease heartburn:**
      i. Increased number of days without daytime or nighttime heartburn
      ii. Increase in the number of days without rescue antacids

c. **For H. pylori:** Renewal requests will be evaluated using criteria from Initial Therapy. Multiple requests for renewal treatment will not be approved and these requests will be forwarded to Utilization Management for review

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
   a. Acute tubulointerstitial nephritis
   b. Severe cutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis
   c. Hypomagnesemia refractory to treatment
   d. Hypocalcemia refractory to treatment

6. Individual is not currently taking any other drugs which may result in a significant drug interaction requiring discontinuation, such as:
   a. Concurrent use with atazanavir or nelfinavir
   b. Moderate or strong CYP3A4 inducers (see Definitions section)

Renewal duration:
12 months: Maintenance of erosive esophagitis
4 weeks: Relief of heartburn associated with non-erosive gastroesophageal reflux disease (NERD)

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Voquezna (vonoprazan) is a potassium-competitive acid blocker indicated for both healing and to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults. Voquezna (vonoprazan) is also indicated for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults in combination with amoxicillin and clarithromycin or in combination with amoxicillin alone.

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 pumps in a noncovalent and reversible manner.

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Gastroesophageal reflux disease (GERD) is a condition that develops when stomach contents are refluxed into the esophagus and cause troublesome symptoms and/or complications. The term GERD covers a spectrum of conditions, including endoscopy-negative GERD (aka NERD), erosive esophagitis (EE), and Barrett's esophagus (BE). GERD may be defined as the presence of at least weekly heartburn and/or regurgitation. Non-erosive gastroesophageal reflux disease (NERD) individuals satisfy the definition of GERD but do not have either BE or definite endoscopic esophageal mucosal breaks (erosions or ulcerations).

The endoscopic classification of EE, utilizing the LA Grade Classification, applies the appearance of a mucosal break, defined as an area of slough or erythema with a sharp line of demarcation from adjacent normal mucosa, in the grading. EE is then graded from "A-D", according to the extent of mucosal break seen on endoscopy. Proton pump inhibitors (PPIs), such as lansoprazole or omeprazole, are effective anti-secretory agents for relieving GERD symptoms, healing the injured mucosa, and maintaining a healed mucosa. However, it is estimated that up to 40% of individuals report suboptimal response to once daily PPI therapy and as such many are prescribed twice daily dosing of PPIs. LA Classification grades C or D (corresponding to moderate to severe EE) have shown suboptimal healing rates of 62% to 84% after 8 weeks of treatment with a PPI. NERD is a non-progressive disease and treatment of NERD is symptom-driven and includes use of PPIs for 4-8 weeks.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Los Angeles Classification of Esophagitis Grading Scale:

LA Grade Classification	
Grade A	One or more mucosal breaks with a length of **no longer** than 5 mm that does not extend between the tops of 2 mucosal folds
Grade B	One or more mucosal breaks with a length of **longer** than 5 mm that does not extend between the tops of 2 mucosal folds
Grade C	One or more mucosal breaks that are continuous between the tops of 2 or more mucosal folds, which involves less than 75% of the circumference
Grade D	One or more mucosal breaks, which involves at least 75% of the circumference
A mucosal break is defined as "an area of slough or erythema with a sharp line of demarcation from adjacent normal mucosa"	

Definitions of Heartburn Severity (Daytime/Nighttime):

Definitions of Daytime Heartburn Severity (Daytime/Awake Time)	
None	No heartburn
Mild	Occasional heartburn, can be ignored, does not influence daily routine
Moderate	Heartburn cannot be ignored and/or occasionally influences daily routine

Severe	Heartburn present most of day and/or regularly influences daily routine
Very severe	Constant heartburn and/or markedly influences daily routine
Definitions of Nighttime Heartburn Severity (Nighttime/Sleep Time)	
None	No heartburn
Mild	Occasional heartburn, can be ignored, does not influence sleep
Moderate	Heartburn cannot be ignored and/or occasionally influences sleep
Severe	Heartburn present most of night and/or regularly influences sleep
Very severe	Constant heartburn and/or markedly influences sleep

Treatment of Gastroesophageal Reflux Disease in Adults:

	Low dose (oral)	Standard dose (oral)	High dose (oral)
Histamine 2 receptor antagonists (H2RA)*			
Cimetidine§	200 mg twice daily	400 mg twice daily Δ	Not recommended
Famotidine	10 mg twice daily	20 mg twice daily Δ	40 mg twice daily
Nizatidine	75 mg twice daily ◊	150 mg twice daily	300 mg twice daily
Proton pump inhibitors (PPIs): (H-K) ATPase Pump			
Dexlansoprazole	Not available	30 mg daily Δ	60 mg once daily or 30 mg twice daily
Esomeprazole	20 mg daily ¥	40 mg daily	40 mg twice daily
Lansoprazole	15 mg daily	30 mg daily	30 mg twice daily
Omeprazole	10 mg daily	20 mg daily	40 mg once daily or 20 mg twice daily
Pantoprazole	20 mg daily	40 mg daily	40 mg twice daily
Rabeprazole	10 mg daily ¥	20 mg daily	20 mg twice daily
Potassium-competitive acid blocker (PCABs): (H-K) ATPase Pump			
Vonoprazan	10 mg once daily	20 mg once daily	20 mg twice daily

* Histamine 2 receptor antagonists require dose adjustment in the setting of renal insufficiency.

Δ The **daily dose for erosive esophagitis with symptoms of GERD** in the US prescribing information **is up to twice the standard dose shown in this table**.

◇ Strength not available in US. Available elsewhere.

§ Significant drug interactions can occur. When initiating or altering drug therapy, use of a drug interactions database, such as the drug interactions program, is advised. Other histamine 2 receptor antagonists with more favorable adverse effect profiles and fewer drug interactions (e.g., famotidine) are generally preferred.

¥ Dose strength limited to certain dosage forms (e.g., granules for oral suspension or sprinkle capsule).

Consult local product availability.

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Risk factors for Barrett's esophagus: (**must** have a duration of GERD of at least 5-10 years)

- Age 50 years or older
- Male sex
- White individuals
- Hiatal hernia
- Obesity
- Nocturnal reflux
- Tobacco use (past or current)
- First-degree relative with Barrett's esophagus and/or adenocarcinoma

Alarm features suggestive of a gastrointestinal malignancy:

- New onset of dyspepsia in patient ≥60 years
- Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
- Iron deficiency anemia
- Anorexia
- Unexplained weight loss
- Dysphagia
- Odynophagia
- Persistent vomiting
- Gastrointestinal cancer in a first-degree relative

Some examples of Cytochrome P450 Interactions: (Not a complete list)

CYP2C19			
Strong Inducer	Moderate Inducer	Strong Inhibitor	Moderate Inhibitor
rifampin	carbamazepine, dabrafenib, enzalutamide, letermovir, phenytoin derivatives, Saint John's wort, tipranavir/ritonavir	delavirdine, fluconazole, fluvoxamine, ticlopidine	armodafinil, cimetidine, eslicarbazepine, esomeprazole, felbamate, fluoxetine, isoniazid, modafinil, omeprazole, oxcarbazepine, voriconazole
CYP3A4			
Strong Inducer	Moderate Inducer	Strong Inhibitor	Moderate Inhibitor
carbamazepine, phenobarbital, phenytoin derivatives, primidone, rifabutin, rifampin, rifapentine, rufinamide, Saint John's wort	armodafinil, bexarotene, bosentan, dabrafenib, deferasirox, dexamethasone, efavirenz, modafinil, nafcillin, nevirapine, oxcarbazepine	clarithromycin, isoniazid, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole	amiodarone, aprepitant, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit juice, isavuconazonium, netupitant, verapamil, zafirlukast

Resources:

Voquezna (vonoprazan) product information, revised by Phathom Pharmaceuticals, Inc. 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Kahrilas PJ. Clinical manifestations and diagnosis of gastroesophageal reflux disease in adults. In: UpToDate, Talley NJ, Swenson S, Meyer C (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated October 16, 2024. Accessed March 13, 2025.

Kahrilas PJ. Initial management of gastroesophageal reflux disease in adults. In: UpToDate, Talley NJ, Swenson S, Meyer C (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated February 21, 2025. Accessed March 13, 2025.

Fass Ronnie. Approach to refractory gastroesophageal reflux disease in adults. In: UpToDate, Talley NJ, Robson KM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated May 14, 2024. Accessed March 13, 2025.

Shah SC, Kao JY, Moss SF. Treatment regimens for Helicobacter pylori in adults. In: UpToDate, Talley NJ, Swenson S, Meyer C (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated March 05, 2025. Accessed March 13, 2025.

Bergsland E, Ge PS. Management and prognosis of Zollinger-Ellison syndrome (gastrinoma). In: UpToDate, Laine L, Shah SM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated December 04, 2024. Accessed March 14, 2025.

Laine L, DeVault K, Katz P, et al.: Vonoprazan Versus Lansoprazole for Healing and Maintenance of Healing of Erosive Esophagitis: A Randomized Trial. Gastroenterology 2023;164(1) :61–71. Accessed February 23, 2024. Re-evaluation March 13, 2025.

Targownik LE, Fisher DA, Saini SD. AGA Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review. Gastroenterology 2022 April; 1 (4); 162:1334–1342. Accessed February 29, 2024. Re-evaluation March 13, 2025.

Katz PO, Dunbar K, Schnoll-Sussman FH, et al.: ACG Clinical Guideline: Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2022 January 01; 117(1): 27–56. Accessed March 04, 2024. Re-evaluation March 13, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04124926: A Phase 3, Randomized, Double-Blind, Two Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients With Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients With Healed Erosive Esophagitis. Available from: http://clinicaltrials.gov. Last update posted July 29, 2022. Last verified July 2022. Accessed February 23, 2024. Re-evaluation March 13, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04124926: Protocol Number: EE-301. A Phase 3, Randomized, Double-Blind, Two Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients With Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients With Healed Erosive Esophagitis. Available from: http://clinicaltrials.gov. October 01, 2019. Accessed February 23, 2024. Re-evaluation March 13, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04167670: A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy With Oral Vonoprazan 20 mg or Double-Blind Triple Therapy With Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy With Oral Lansoprazole 30 mg Daily in Patients With Helicobacter Pylori Infection. Available from: http://clinicaltrials.gov. Last update posted April 05, 2022. Last verified March 2022. Accessed February 23, 2024. Re-evaluation March 13, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04167670: Protocol Number: HP-301. A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy With Oral Vonoprazan 20 mg or Double-Blind Triple Therapy With Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy With Oral Lansoprazole 30 mg Daily in Patients With Helicobacter Pylori Infection. Available from: http://clinicaltrials.gov. Last update posted April 05, 2022. Last verified March 2022. Accessed February 23, 2024. Re-evaluation March 13, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT05195528: A Phase 3, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg Compared to Placebo for Relief of Heartburn in Subjects With Symptomatic Non-Erosive Gastroesophageal Reflux Disease (NERD) After 4 Weeks and to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg for Relief of Heartburn in Subjects With NERD After 6 Months. Available from: http://clinicaltrials.gov. Last update posted December 29, 2023. Last verified December 2023. Accessed March 14, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT05195528: Protocol Number: NERD-301. A Phase 3, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg Compared to Placebo for Relief of Heartburn in Subjects With Symptomatic Non-Erosive Gastroesophageal Reflux Disease (NERD) After 4 Weeks and to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg for Relief of Heartburn in Subjects With NERD After 6 Months. Available from: http://clinicaltrials.gov. Last update posted December 29, 2023. Last verified December 2023. Accessed March 14, 2025.