PDL DRUG REVIEW

Proprietary Name: Voquezna®
Common Name: vonoprazan
PDL Category: Gastrointestinal Agents

Comparable Products	Preferred Drug List Status
Lansoprazole	Preferred
Omeprazole	Preferred
Pantoprazole	Preferred

Pharmacology/Usage: Vonoprazan, the active ingredient of Voquezna®, is a potassium-competitive acid blocker. It 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 (PPI), in that it blocks the final step of acid production. Vonoprazan does not require activation by acid. It may selectively concentrate in the parietal cells in both the resting and stimulated states. Vonoprazan binds to the active pumps in a non-covalent and reversible manner.

Indication:

- For healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
- To maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
- In combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults.
- In combination with amoxicillin for the treatment of *H. pylori* infection in adults.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate and well-controlled studies of use in pregnant women. Available data with vonoprazan-containing products use in pregnant women are not sufficient to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Report pregnancies to the Phathom Pharmaceuticals, Inc. Adverse Event reporting line at 1-888-775-7428. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 10mg, 20mg.

Recommended Dosage: Take Voquezna® with or without food. Swallow tablets whole; do not chew or crush the tablets.

Regarding missed doses, for the healing or maintenance of healed erosive esophagitis, if a dose is missed administer Voquezna® as soon as possible within 12 hours after the missed dose. If more than 12 hours have passed, skip the missed dose and administer the next dose at the regularly scheduled time. For the treatment of *H. pylori* infection, if a dose is missed, administer Voquezna® as soon as possible within 4 hours after the missed dose. If more than 4 hours have passed, skip the missed dose and administer the next dose at the regularly scheduled time.

For healing of erosive esophagitis and relief of heartburn, the recommended adult dosage is 20mg QD for 8 weeks. *For maintenance of healed erosive esophagitis and relief of heartburn*, the recommended adult dosage is 10mg QD for up to 6 months.

For treatment of H. pylori infection:

- *Triple therapy:* The recommended adult dosage is Voquezna® 20mg plus amoxicillin 1,000mg plus clarithromycin 500mg, each given BID (in the morning and evening, 12 hrs apart) for 14 days.
- *Dual Therapy:* The recommended adult dose is Voquezna® 20mg BID (morning and evening) plus amoxicillin 1,000mg TID (morning, mid-day, and evening) for 14 days.
- Also refer to the amoxicillin and clarithromycin full prescribing information.

The recommended dosage of Voquezna® in adults with renal impairment is described in the tables below, which were adapted from the prescribing information.

The recommended Voquezna® dosage for healing of erosive esophagitis in patients with renal impairment:

eGFR	Recommended dosage
30ml/min or greater	20mg QD
Less than 30ml/min	10mg QD

The recommended dosage of Voquezna® for maintenance of healed erosive esophagitis in adults with renal impairment is the same as for adults with normal renal function.

The recommended dosage of Voquezna® for treatment of *H. pylori* infection in adults with renal impairment:

eGFR	Recommended dosage
30ml/min or greater	20mg BID
Less than 30ml/min	Use not recommended

The recommended dosage of Voquezna® in adults with hepatic impairment is described in the tables below, which were adapted from the prescribing information.

The recommended Voquezna® dosage for healing of erosive esophagitis in adult patients with hepatic impairment:

Classification	Recommended dosage
Child-Pugh Class A	20mg QD
Child-Pugh Class B	10mg QD
Child-Pugh Class C	10mg QD

The recommended dosage of Voquezna® for maintenance of healed erosive esophagitis in adults with hepatic impairment is the same as for patients with normal hepatic function.

The recommended Voquezna® dosage for treatment of *H. pylori* infection in adult patients with hepatic impairment:

Classification	Recommended dosage
Child-Pugh Class A	20mg BID
Child-Pugh Class B	Use not recommended
Child-Pugh Class C	Use not recommended

Drug Interactions: The information discussed below include drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with Voquezna® and instructions for preventing or managing them. Consult the labeling of concomitantly used drugs to obtain further information about interactions with vonoprazan.

Vonoprazan reduces intragastric acidity, which may alter the absorption of antiretroviral drugs leading to changes in the safety and/or efficacy. Concomitant use of Voquezna® with rilpivirine-containing products is contraindicated. Avoid concomitant use of Voquezna® with atazanavir and nelfinavir. See the prescribing information of other antiretroviral drugs dependent on gastric pH for absorption prior to concomitant use with Voquezna®.

As mentioned, vonoprazan reduces intragastric acidity, which may decrease the absorption of drugs reducing their efficacy (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole). See the prescribing information for other drugs dependent on gastric pH for absorption.

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions, including potentially fatal arrhythmias, and are contraindicated. Amoxicillin also has drug interactions. See contraindications and warnings/precautions in the prescribing information for clarithromycin, and see drug interactions in the prescribing information for amoxicillin.

Vonoprazan is a weak CYP3A inhibitor. Vonoprazan may increase exposure of CYP3A4 substrates, which may increase the risk of adverse reactions related to these substrates. Monitor frequently for concentrations and/or adverse reactions related to the substrate drugs when used with Voquezna.® Dosage reduction of substrate drugs may be needed.

Vonoprazan is a CYP2C19 inhibitor and may reduce plasma concentrations of the active metabolite of clopidogrel and may cause reduction in platelet inhibition. In addition, it may increase exposure of CYP2C19 substrates (e.g., citalopram, cilostazol). Carefully monitor the efficacy of clopidogrel if use concomitantly with Voquezna® and consider alternative anti-platelet therapy. In addition, carefully monitor patients for adverse reactions associated with citalopram and cilostazol. See the prescribing information for dosage adjustments.

Vonoprazan reduces intragastric acidity, which increases chromogranin A (CgA) levels and may cause false positive results in diagnostic investigations for neuroendocrine tumors. Assess CgA levels at least 14 days after stopping Voquezna® treatment and repeat the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), use the same commercial laboratory for testing, as reference ranges between tests may vary.

Vonoprazan is a CYP3A substrate. Avoid concomitant use of Voquezna® with strong or moderate CYP3A4 inducers.

Box Warning: There is no box warning with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Voquezna® 20mg QD) minus reported incidence for lansoprazole 30mg QD in adults with erosive esophagitis (healing phase).* The most frequently reported adverse events included gastritis (1%), diarrhea (0%), abdominal distension (1%), abdominal pain (1%), and nausea (1%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Voquezna® 10mg QD) minus reported incidence for lansoprazole 15mg QD in adults with erosive esophagitis (maintenance phase). The most frequently reported adverse events included gastritis (3%), abdominal pain (2%), dyspepsia (1%), hypertension (1%), and urinary tract infection (1%).

In adults, symptomatic response to Voquezna® does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in patients who have a suboptimal response or an early symptomatic relapse after completing treatment with Voquezna®.

Acute tubulointerstitial nephritis (TIN) has been reported with Voquezna®. If suspected, discontinue Voquezna®.

Published observational studies suggest that PPIs may be associated with an increased risk of *Clostridioides difficile*-associated diarrhea (CDAD), especially in hospitalized patients. Voquezna® may also increase the risk of CDAD. Consider CDAD in patients with diarrhea that does not improve. Use the shortest duration of Voquezna® appropriate to the condition being treated.

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose and long-term therapy (a year or longer). Bone fracture, including osteoporosis-related fracture, has also been reported with vonoprazan. Use the shortest duration of Voquezna® appropriate to the condition being treated.

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with Voquezna®. Discontinue Voquezna® at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Long-term use of acid-suppressing drugs can lead to malabsorption of vitamin B12. Vitamin B12 deficiency has been reported post marketing with vonoprazan. If clinical symptoms consistent with vitamin B12 deficiency are observed in patients treated with Voquezna®, consider further workup.

Hypomagnesemia has been reported post marketing with vonoprazan. Consider monitoring magnesium levels prior to the start of Voquezna® and periodically in patients expected to be on prolonged treatment, in patients taking drugs that may have increased toxicity in the presence of hypomagnesemia, or drugs that may cause hypomagnesemia. Treatment of hypomagnesemia may require magnesium replacement and discontinuation of Voquezna®. Consider monitoring magnesium and calcium levels prior to starting treatment and periodically while on treatment in patients with a pre-existing risk of hypocalcemia. Supplement with magnesium and/or calcium, as necessary.

Use of Voquezna® is associated with a risk of fundic gland polyps that increases with long-term use, especially beyond one year. Fundic gland polyps have been reported with vonoprazan in clinical trials and post marketing use with PPIs. Most who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of Voquezna® appropriate to the condition being treated.

Contraindications:

- In patients with a known hypersensitivity to vonoprazan or any component of the product.
- With rilpivirine-containing products.

- For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with Voquezna®, refer to the Contraindications section of the corresponding prescribing information.

Manufacturer: Phathom Pharmaceuticals

Analysis: The safety and efficacy of Voquezna® *for the healing of erosive esophagitis and relief of heartburn* were assessed in a randomized, active-controlled, double-blind, eight-week study conducted in the US and Europe that included adults (N=1024) with endoscopically confirmed erosive esophagitis. Severity of the disease was classified per the Los Angeles (LA) Classification Grading System (Grades A through D). Patients were randomized to either Voquezna® 20mg QD or lansoprazole 30mg QD for 2 to 8 weeks. Patients who were positive for *H. pylori* infection or who had Barrett's esophagus and/or definite dysplastic changes in the esophagus at baseline were excluded from the study.

Per LA Classification, 66% had mild erosive esophagitis (Grades A or B) and 34% had moderate to severe erosive esophagitis (Grades C or D) prior to randomization. Patients in the trial had a mean age of 51 years (range 18 to 84), while 53% were female and 91% were white.

Healing of erosive esophagitis was assessed at week 2 and week 8 and resolution of heartburn symptoms was assessed daily over the 8 week period. If endoscopic healing of erosive esophagitis was confirmed at week 2, the patient entered the maintenance phase of the study. If endoscopic healing was not confirmed at week 2, the patient continued to receive randomized treatment until week 8. Only patients with confirmed endoscopic healing entered the maintenance phase. All endoscopies were centrally read and adjudicated.

The primary endpoint was endoscopically confirmed complete healing of all grades of erosive esophagitis at week 2 or week 8. Results are presented in the table below, which was adapted from the prescribing information.

	Treatment Group		Treatment difference
Timepoint	Voquezna® 20mg QD (N=514)	Lansoprazole 30mg QD (N=510)	
Week 2 or 8	93%	85%	8[1]
Week 2	74%	68%	

[1] Demonstrated non-inferiority to lansoprazole

For the secondary endpoint of complete healing of erosive esophagitis at week 2, superiority was demonstrated in the subgroup of patients with LA Grade C or D disease, with 70% of 177 Voquezna® treated patients and 53% of 174 lansoprazole treated patients who achieved healing (18% treatment difference).

Complete healing of erosive esophagitis at either week 2 or week 8 in the subgroup of patients with LA Grade C or D disease was 92% in patients treated with Voquezna® and 72% in patients treated with lansoprazole. This endpoint was not statistically significant under the prespecified multiple testing procedure.

The percentage of 24-hour heartburn-free days through week 8 was assessed as a secondary endpoint. Results are presented in the table below, which was adapted from the prescribing information.

	Treatment Group		Treatment difference
Parameter	Voquezna® 20mg QD (N=514)	Lansoprazole 30mg QD (N=510)	
Mean	67%	64%	3[1]
Median	81%	78%	

[1] Demonstrated non-inferiority to lansoprazole

Two additional randomized, active-controlled, double-blind studies conducted outside of the United States, of similar design to the US trial, also demonstrated non-inferiority of vonoprazan 20mg QD compared to lansoprazole 30mg QD for the primary endpoint of healing of all grades of erosive esophagitis by week 8.

The maintenance of healed erosive esophagitis and relief of heartburn was assessed. Patients who completed the healing phase of the erosive esophagitis study and demonstrated endoscopically confirmed healed erosive esophagitis at week 2 or week 8 were re-randomized in the maintenance phase to either Voquezna® 10mg QD, a higher dosage of Voquezna®, or lansoprazole 15mg QD. Maintenance of healing and resolution of heartburn symptoms were assessed over 24 weeks. The higher Voquezna® dose group did not demonstrate additional treatment benefit compared to Voquezna® 10mg QD.

The primary endpoint was maintenance of healed erosive esophagitis (all grades) through week 24. A secondary endpoint was maintenance of healed erosive esophagitis in the subgroup of patients with LA Grade C or D disease prior to randomization in the healing phase of the study. Results are presented in the table below, which was adapted from the prescribing information.

	Treatment Group		Treatment difference
Baseline Severity	Voquezna® 10mg QD	Lansoprazole 15mg QD	
All LA Grades:	N=293	N=294	
Week 24	79%	72%	7[1]
LA Grade C or D:	N=95	N=96	
Week 24	75%	61%	13[2]

[1] Demonstrated non-inferiority and superiority to lansoprazole [2]Demonstrated superiority to lansoprazole

The percentage of 24-hour heartburn-free days through week 24 was evaluated for non-inferiority as a secondary endpoint. Results are presented in the table below, which was adapted from the prescribing information.

	Treatment Group		Treatment difference
Parameter	Voquezna® 10mg QD (N=293)	Lansoprazole 15mg QD (N=294)	
Mean	81%	79%	2[1]
Median	95%	89%	

[1] Demonstrated non-inferiority to lansoprazole

Two additional randomized, active-controlled, double-blind studies conducted outside of the U.S., of similar design to the U.S. trial, also demonstrated non-inferiority of vonoprazan 10mg QD compared to

lansoprazole 15mg QD for the primary endpoint of maintenance of healed erosive esophagitis (all grades) through week 24.

The use in the *treatment of H. pylori infection* was assessed. The safety and efficacy of Voquezna®, amoxicillin, and clarithromycin (triple therapy) and Voquezna® and amoxicillin (dual therapy) were assessed in a randomized, controlled, double-blind (triple therapy)/open-label (dual therapy) study conducted in the US and Europe in treatment-naïve *H. pylori*-positive adults with at least one clinical condition, including 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. Patients were randomized to one of the following regimens administered for 14 consecutive days, including:

- Voquezna® 20mg BID, plus amoxicillin 1,000mg BID, and clarithromycin 500mg BID (N=346).
- Voquezna® 20mg BID and amoxicillin 1,000mg TID (N=348).
- Lansoprazole 30mg BID, amoxicillin 1,000mg BID, and clarithromycin 500mg BID (N=345).

H. pylori infection at baseline was defined as positive by ^{13}C urea breath test (UBT) and follow-up upper endoscopy (culture or histology). *H. pylori* eradication was confirmed with a negative ^{13}C UBT test-of-cure at least 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. Patients in the treatment groups had a mean age of 51 years (range 20 to 87 years), while 62% were female, and 89% were white.

Voquezna®, amoxicillin, and clarithromycin and Voquezna® and amoxicillin were shown to be non-inferior to lansoprazole, amoxicillin, and clarithromycin in patients who did not have a clarithromycin or amoxicillin resistant strain of *H. pylori* at baseline. Voquezna®, amoxicillin, and clarithromycin and Voquezna® and amoxicillin were shown to be superior to lansoprazole, amoxicillin, and clarithromycin in patients who had a clarithromycin resistant strain of *H. pylori* at baseline and in the overall population. *H. pylori* eradication rates at least 27 days post-therapy are presented in the table below, which was adapted from the prescribing information.

	Voquezna®, amoxicillin & clarithromycin % (n)	Voquezna® & amoxicillin % (n)	Lansoprazole, amoxicillin & clarithromycin (LAC) % (n)
Patients with *H. pylori* infection who did not have a clarithromycin or amoxicillin resistant strain at baseline	85% (222)	79% (208)	79% (201)
Treatment difference from LAC	6%[1]	-0.3%[2]	
All randomized patients with *H. pylori* infection at baseline	81% (273)	77% (250)	69% (226)
Treatment difference from LAC	12%[3]	9%[4]	
Patients with *H. pylori* infection who had a clarithromycin resistant strain of *H. pylori* at baseline	66% (48)	70% (39)	32% (23)
Treatment difference from LAC	34%[5]	38%[5]	

[1] p<0.0001 for test of non-inferiority vs LAC [2]p<0.01 for test of non-inferiority vs LAC [3]p=0.0003 for test of superiority vs LAC
[4] p=0.01 for test of superiority vs LAC [5]p<0.0001 for test of superiority vs LAC

Place in Therapy: Voquezna® is a potassium-competitive acid blocker indicated for healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults; to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults; in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults; and in combination with amoxicillin for the treatment of *H. pylori* infection in adults. The safety and efficacy of treatment were assessed for each indication. For the healing of erosive esophagitis and relief of heartburn, Voquezna® was non-inferior to lansoprazole for the rates of healing of all LA grades of erosive esophagitis at week 2 or 8 and for the percentage of 24-hour heartburn-free days in patients with erosive esophagitis. For maintenance of healed erosive esophagitis, the maintenance rates with Voquezna® 10mg were non-inferior and superior to lansoprazole 15mg QD for all LA grades, and was superior to lansoprazole for LA grade C or D. With the relief of heartburn during maintenance of healed erosive esophagitis, Voquezna® demonstrated non-inferiority to lansoprazole. When Voquezna® was evaluated in patients with *H. pylori*®, Voquezna® plus amoxicillin and clarithromycin as well as Voquezna® and amoxicillin were superior to lansoprazole, amoxicillin, and clarithromycin in the overall population and in patients who had a clarithromycin resistant strain of *H. pylori* at baseline. Voquezna® is a first-in-class treatment that offers providers another treatment option.

Summary

There is some evidence at this time from a phase 3 study to suggest that Voquezna® (as triple or dual therapy) may be more effective than lansoprazole (as triple therapy) for treatment of *H. pylori* infection, and that Voquezna® may be more effective than lansoprazole in maintenance of healed erosive esophagitis. However, there is no evidence at this time to support that Voquezna® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Voquezna® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Voquezna® [package insert]. Buffalo Grove, IL: Phathom Pharmaceuticals, Inc; 2023.