HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VOQUEZNA® safely and effectively. See full prescribing information for VOQUEZNA.

VOQUEZNA (vonoprazan) tablets, for oral use
Initial U.S. Approval: 2022

INDICATIONS AND USAGE
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. (1)
• to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults. (1)
• in combination with amoxicillin and clarithromycin for the treatment of Helicobacter pylori (H. pylori) infection in adults. (1)
• in combination with amoxicillin for the treatment of H. pylori infection in adults. (1)

DOSAGE AND ADMINISTRATION
Recommended Dosage:
• Healing of Erosive Esophagitis: 20 mg once daily for 8 weeks. (2.1)
• Maintenance of Healed Erosive Esophagitis: 10 mg once daily for up to 6 months. (2.1)
• Treatment of H. pylori Infection: see full prescribing information. (2.1)
• See also full prescribing information for the recommended dosage by indication for patients with renal or hepatic impairment. (2.2, 2.3)

Administration Instructions:
• Take with or without food. (2.4)
• Swallow whole; do not chew or crush. (2.4)

DOSAGE FORMS AND STRENGTHS
Tablets: 10 mg and 20 mg of vonoprazan. (3)

CONTRAINDICATIONS
• Gastric Malignancy: Symptomatic response to treatment does not preclude the presence of gastric malignancy; consider additional follow-up and diagnostic testing. (5.1)
• Acute Tubulointerstitial Nephritis: Discontinue treatment and evaluate patients. (5.2)
• Clostridioides difficile-Associated Diarrhea (CDAD): May be associated with an increased risk; use the shortest duration of treatment appropriate to the condition. (5.3)

WARNINGS AND PRECAUTIONS
• Presence of Gastric Malignancy: Symptomatic response to treatment does not preclude the presence of gastric malignancy; consider additional follow-up and diagnostic testing. (5.1)
• Bone Fracture, including Osteoporosis-related Fracture: Use the shortest duration of treatment appropriate to the condition. (5.4)
• Severe Cutaneous Adverse Reactions: Discontinue at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation. (5.5)
• Vitamin B12 (Cobalamin) Deficiency: Long-term use may lead to malabsorption or deficiency; consider further workup if clinical symptoms are present. (5.6)
• Hypomagnesemia and Mineral Metabolism: Consider monitoring magnesium levels prior to starting treatment and periodically if prolonged treatment is expected, or if concomitant use of digoxin or other drugs that cause hypomagnesemia. (5.7)
• Interactions with Investigations for Neuroendocrine Tumors: Increased chromogranin A (CgA) levels may interfere with diagnostic investigations; temporarily stop VOQUEZNA at least 14 days before assessing CgA levels. (5.8, 7)
• Fundic Gland Polyps: Risk increases with long-term use; use the shortest duration of treatment appropriate to the condition. (5.9)

ADVERSE REACTIONS
Most common adverse reactions in VOQUEZNA-treated patients are:
• Healing of Erosive Esophagitis (≥25%): gastritis, diarrhea, abdominal distension, abdominal pain, and nausea. (6.1)
• Maintenance of Healed Erosive Esophagitis (≥3%): gastritis, abdominal pain, dyspepsia, hypertension, and urinary tract infection. (6.1)
• Treatment of H. pylori Infection (≥2%): diarrhea, dysgeusia, vulvovaginal candidiasis, abdominal pain, headache, hypertension, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Phathom Pharmaceuticals, Inc. at toll-free phone 1-888-775-7428 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
See full prescribing information for a list of clinically important drug interactions. (7)

USE IN SPECIFIC POPULATIONS
Lactation: Breastfeeding not recommended during treatment. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 11/2023

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2.2 Recommended Dosage in Patients with Renal Impairment
2.3 Recommended Dosage in Patients with Hepatic Impairment
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5 WARNINGS AND PRECAUTIONS
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1 INDICATIONS AND USAGE
VOQUEZNA is 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.
• in combination with amoxicillin for the treatment of H. pylori infection in adults.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
Healing of Erosive Esophagitis and Relief of Heartburn
• The recommended adult oral dosage is VOQUEZNA 20 mg once daily for 8 weeks.

2.2 Recommended Dosage in Patients with Renal Impairment
2.3 Recommended Dosage in Patients with Hepatic Impairment
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Maintenance of Healed Erosive Esophagitis and Relief of Heartburn
• The recommended adult oral dosage is VOQUEZNA 10 mg once daily for up to 6 months.

Treatment of H. pylori Infection
• Triple Therapy: The recommended adult oral dosage is VOQUEZNA 20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each given twice daily (in the morning and evening, 12 hours apart) for 14 days.
• Dual Therapy: The recommended adult oral dose is VOQUEZNA 20 mg given twice daily (in the morning and evening) plus amoxicillin 1,000 mg three times daily (in the morning, mid-day, and evening) for 14 days.
• Also refer to the amoxicillin and clarithromycin full prescribing information.

2.2 Recommended Dosage in Patients with Renal Impairment
Healing of Erosive Esophagitis
The recommended dosage of VOQUEZNA in adult patients with renal impairment is described in Table 1 below [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].
Table 1: Recommended VOQUEZNA Dosage in Patients with Renal Impairment: Healing of Erosive Esophagitis

<table>
<thead>
<tr>
<th>Estimated glomerular filtration rate (GFR)</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mL/minute or greater</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>Less than 30 mL/minute</td>
<td>10 mg once daily</td>
</tr>
</tbody>
</table>

Maintenance of Healed Erosive Esophagitis
The recommended dosage of VOQUEZNA in adult patients with renal impairment is the same as for adult patients with normal renal function [see Dosage and Administration (2.1)].

Treatment of H. pylori Infection
The recommended dosage of VOQUEZNA in adult patients with renal impairment is described in Table 2 below [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

Table 2: Recommended VOQUEZNA Dosage in Patients with Renal Impairment: Treatment of H. pylori Infection

<table>
<thead>
<tr>
<th>Estimated GFR</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mL/minute or greater</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>Less than 30 mL/minute</td>
<td>Use is not recommended</td>
</tr>
</tbody>
</table>

* Also refer to the Dosage and Administration section of the amoxicillin and clarithromycin prescribing information for dosage recommendations in patients with renal impairment.

2.3 Recommended Dosage in Patients with Hepatic Impairment

Healing of Erosive Esophagitis
The recommended dosage of VOQUEZNA in adult patients with hepatic impairment is described in Table 3 below [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

Table 3: Recommended VOQUEZNA Dosage in Patients with Hepatic Impairment: Healing of Erosive Esophagitis

<table>
<thead>
<tr>
<th>Classification</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh Class A</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>Child-Pugh Class B</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Child-Pugh Class C</td>
<td>10 mg once daily</td>
</tr>
</tbody>
</table>

Maintenance of Healed Erosive Esophagitis
The recommended dosage of VOQUEZNA in adult patients with hepatic impairment is the same as for patients with normal hepatic function [see Dosage and Administration (2.1)].

Treatment of H. pylori Infection
The recommended dosage of VOQUEZNA in adult patients with hepatic impairment is described in Table 4 below [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

Table 4: Recommended VOQUEZNA Dosage in Patients with Hepatic Impairment: Treatment of H. pylori Infection

<table>
<thead>
<tr>
<th>Classification</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh Class A</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>Child-Pugh Class B</td>
<td>Use is not recommended</td>
</tr>
<tr>
<td>Child-Pugh Class C</td>
<td>Use is not recommended</td>
</tr>
</tbody>
</table>

2.4 Administration Instructions
- Take VOQUEZNA with or without food [see Clinical Pharmacology (12.3)].
- Swallow VOQUEZNA tablets whole; do not chew or crush the tablet.
- 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. Continue the normal dosing schedule until the treatment is completed.

3 DOSAGE FORMS AND STRENGTHS

Tablets:
- 10 mg of vonoprazan: pale yellow, oval, film-coated tablets debossed V10 on one side and plain on the other side.
- 20 mg of vonoprazan: pale red, oval, film-coated tablets debossed V20 on one side and plain on the other side.

4 CONTRAINDICATIONS

VOQUEZNA is contraindicated in patients with a known hypersensitivity to vonoprazan or any component of VOQUEZNA. Reactions have included anaphylactic shock [see Adverse Reactions (6.2) and Description (11)].

VOQUEZNA is contraindicated with rifampin-containing products [see Drug Interactions (7)].

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.

5 WARNINGS AND PRECAUTIONS

5.1 Presence of Gastric Malignancy
In adults, symptoms of response to therapy with 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. In older patients, also consider endoscopy.

5.2 Acute Tubulointerstitial Nephritis
Acute tubulointerstitial nephritis (TIN) has been reported with VOQUEZNA [see Adverse Reactions (6.1)]. If suspected, discontinue VOQUEZNA and evaluate patients with suspected acute TIN.

5.3 Clostridioides difficile-Associated Diarrhea
Published observational studies suggest that proton pump inhibitors (PPIs) may be associated with an increased risk of Clostridioides difficile-associated diarrhea (CDAD), especially in hospitalized patients. VOQUEZNA, another drug that blocks the proton pump to inhibit gastric acid production, may also increase the risk of CDAD. Consider CDAD in patients with diarrhea that does not improve [see Adverse Reactions (6.2)]. Use the shortest duration of VOQUEZNA appropriate to the condition being treated.

CDAD has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with VOQUEZNA, refer to Warnings and Precautions section of the corresponding prescribing information.

5.4 Bone Fracture
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, defined as multiple daily doses, 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 [see Dosage and Administration (2.1)]. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines.

5.5 Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with VOQUEZNA [see Adverse Reactions (6.2)].

Discontinue VOQUEZNA at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

5.6 Vitamin B12 (Cobalamin) Deficiency
Long-term use of acid-suppressing drugs can lead to malabsorption of Vitamin B12 caused by hypo- or achlorhydria. Vitamin B12 deficiency has been reported postmarketing with vonoprazan [see Adverse Reactions (6.2)]. If clinical symptoms consistent with Vitamin B12 deficiency are observed in patients treated with VOQUEZNA consider further workup.

5.7 Hypomagnesemia and Mineral Metabolism
Hypomagnesemia has been reported postmarketing with vonoprazan [see Adverse Reactions (6.2)]. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia and may exacerbate underlying hypocalcemia in at-risk patients. Consider monitoring magnesium levels prior to initiation of VOQUEZNA and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium, as necessary. If hypocalcemia is refractory to treatment, consider discontinuing VOQUEZNA.

Consider monitoring magnesium and calcium levels prior to initiation of VOQUEZNA and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium, as necessary. If hypocalcemia is refractory to treatment, consider discontinuing VOQUEZNA.

5.8 Interactions with Diagnostic Investigations for Neuromodendritic 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. Temporarily discontinue VOQUEZNA treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA workup.

If serum CgA concentration increases during therapy, consider temporarily discontinuing VOQUEZNA and retesting CgA levels. Consider repeating CgA levels if an increase occurs during therapy. Consider endoscopy in patients who have a suboptimal response or an early symptomatic relapse after completing treatment with VOQUEZNA. In older patients, also consider endoscopy.

5.9 Fundic Gland Polyps
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 postmarketing use with PPIs. Most patients 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 [see Dosage and Administration (2.1)].
The safety of VOQUEZNA was evaluated in a randomized, active-controlled, double-blind phase are presented in Table 5.

### Table 5: Adverse Reactions in a Clinical Trial of Adult Patients with All Grades of Erosive Esophagitis (2 to 8 Week Healing Phase)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VOQUEZNA 20 mg Once Daily N=514</th>
<th>Lansoprazole 30 mg Once Daily N=510</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 2</td>
<td></td>
</tr>
<tr>
<td>Diarrheac</td>
<td>2 3</td>
<td></td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2 1</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 1</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2 1</td>
<td></td>
</tr>
</tbody>
</table>

- <sup>a</sup> Reported in at least 2% of patients in the VOQUEZNA arm.
- <sup>b</sup> The trial was not designed to support comparative claims for VOQUEZNA for the adverse reactions reported in this table.
- <sup>c</sup> Represents a grouped term and includes related terms.

Adverse reactions reported in at least 3% of patients in the VOQUEZNA arm in the healing phase are presented in Table 5.

### Table 6: Adverse Reactions in a Clinical Trial of Adult Patients with All Grades of Erosive Esophagitis (24 Week Maintenance Phase)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VOQUEZNA 10 mg Once Daily N=296</th>
<th>Lansoprazole 15 mg Once Daily N=297</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6 3</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4 2</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4 3</td>
<td></td>
</tr>
<tr>
<td>Hypertension&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 2</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 2</td>
<td></td>
</tr>
</tbody>
</table>

- <sup>a</sup> Reported in at least 3% of patients in the VOQUEZNA arm.
- <sup>b</sup> The trial was not designed to support comparative claims for VOQUEZNA for the adverse reactions reported in this table.
- <sup>c</sup> Represents a grouped term and includes related terms.

Other Clinical Trials of Erosive Esophagitis

Adverse reactions reported in the United States trial were similar to those reported in 4 additional randomized, active-controlled, double-blind studies of vonoprazan compared to lansoprazole conducted outside of the United States (two eight-week trials of healing of erosive esophagitis and two 24-week maintenance of healed erosive esophagitis trials).

### Less Common Adverse Reactions

Adverse reactions reported in 1% or less of VOQUEZNA-treated patients in the healing or maintenance phase of the United States trial are:

- **Blood and lymphatic system disorders:** anemia, lymphocytosis
- **Cardiac disorders:** tachycardia
- **Ear and labyrinth disorders:** vertigo
- **Gastrointestinal disorders:** duodenal polyp, dry mouth, dysphagia, eructation, flatulence, gastric polyps, vomiting
- **General disorders and administrative site conditions:** asthenia, peripheral edema
- **Infections and infestations:** upper respiratory infection
- **Investigations:** increased liver function test
- **Metabolism and nutritional disorders:** diabetes mellitus
- **Musculoskeletal system:** bone fracture
- **Nervous system disorders:** dizziness, headache, syncope
- **Psychiatric disorders:** depression, insomnia
- **Renal and urinary disorders:** tubulointerstitial nephritis
- **Skin and subcutaneous tissue disorders:** eczema, rash, urticaria

### Table 7: Adverse Reactions in Adult Patients with H. pylori Infection

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VOQUEZNA and Amoxicillin N=348</th>
<th>VOQUEZNA, Amoxicillin, and Clarithromycin N=346</th>
<th>Lansoprazole, Amoxicillin, and Clarithromycin N=345</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>5 4 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 5 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal candidiasis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 3 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 2 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 3 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 3 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 &lt;1 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- <sup>a</sup> Reported in at least 2% of patients in any treatment arm.
- <sup>b</sup> These trials were not designed to support comparative claims for VOQUEZNA-containing treatment arms for the adverse reactions reported in this table.
- <sup>c</sup> Represents a grouped term and includes related terms.

Other adverse reactions reported in less than 2% of patients treated with VOQUEZNA, amoxicillin, and clarithromycin or VOQUEZNA and amoxicillin are listed below by body system:

- **Blood and lymphatic system disorders:** anemia, leukocytosis, leukopenia, neutropenia
- **Cardiac disorders:** QT prolongation, tachycardia
- **Eye disorders:** orbital edema
- **Gastrointestinal disorders:** abdominal distension, constipation, dry mouth, duodenal polyp, duodenal ulcer, dyspepsia, flatulence, gastric ulcer, gastroesophageal reflux disease, hematochezia, large intestine polyp, rectal polyp, nausea, stomatitis, tongue discomfort, vomiting
- **General disorders and administration site conditions:** fatigue, pyrexia
- **Immune system disorders:** drug hypersensitivity
- **Infections and infestations:** anal fungal infection, gastrointestinal viral infection, oral fungal infection, pneumonia, tongue fungal infection, upper respiratory tract infection, urinary tract infection, viral infection
- **Investigations:** increased liver function test
- **Metabolism and nutrition disorders:** decreased appetite
- **Musculoskeletal system:** bone fracture
- **Nervous system disorders:** ageusia, dizziness, tension headache
- **Psychiatric disorders:** anxiety, depression, insomnia
- **Renal and urinary disorders:** renal hypertrophy, tubulointerstitial nephritis
- **Reproductive system and breast disorders:** vaginal discharge
- **Respiratory, thoracic and mediastinal disorders:** cough, nasal polyps, oropharyngeal pain
- **Skin and subcutaneous tissue disorders:** dermatitis, dry skin, rash

For more information on adverse reactions and laboratory changes with amoxicillin or clarithromycin, refer to ADVERSE REACTIONS section of the corresponding prescribing information.

### 6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of vonoprazan outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Vonoprazan is a CYP3A substrate. Strong or moderate CYP3A inducers decrease vonoprazan exposure [see Clinical Pharmacology (12.3)], which may reduce the effectiveness of VOQUEZNA.

<table>
<thead>
<tr>
<th>Clinical Effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.</td>
<td>Temporarily stop VOQUEZNA at least 14 days before assessing to allow gastrin levels to return to baseline [see Clinical Pharmacology (12.2)].</td>
</tr>
</tbody>
</table>

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

There are no adequate and well-controlled studies of vonoprazan in pregnant women. Available data from pharmacovigilance reports with vonoprazan-containing products use in pregnant women are not sufficient to evaluate for a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

In pregnant rats, no adverse effects were noted after oral administration of vonoprazan during organogenesis at approximately 27-times the maximum recommended human dose (MRHD) based on AUC exposure comparisons.

In a pre- and postnatal development (PPND) study, pups from dams orally administered vonoprazan during organogenesis and through lactation, exhibited liver discoloration, which in follow-up mechanistic animal studies was associated with necrosis, fibrosis, and hemorrhage at a dose approximately 22-times the MRHD based on AUC comparisons which were likely attributable to exposure during lactation [see Use in Specific Populations (8.2)]. These effects were not observed at the next lower dose in this study, which was approximately equal to the MRHD based on AUC comparison, however they were seen at clinically relevant exposures in dose range finding studies in rats [see Data].

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Report pregnancies to the Phathom Pharmaceuticals, Inc. Adverse Event reporting line at 1-888-775-7428.

**Data**

**Animal Data**

Pregnant rats were orally administered vonoprazan at doses of 30, 100, or 300 mg/kg/day (7-, 27-, 130-times the MRHD based on AUC comparison at the same doses from unmedicated female rats from separate studies) during the period of organogenesis from gestation day (GD) 6 to 17. During maternal dosing, one high-dose female died and decreased body weight gain was observed in the highest dose group. Fetal abnormalities were limited to the 300 mg/kg/day and included ventricular septal defect and mal-positioned subclavian artery in fetuses in a majority (15/19) of litters, as well as tail abnormalities and small anal opening. No adverse embryo-fetal effects were observed at the 100 mg/kg/day.

Pregnant rabbits were orally administered vonoprazan at doses of 3, 10, or 30 mg/kg/day (0.04-, 1.5-, 10-times the MRHD based on AUC comparison) from GD 6 to lactation day (LD) 21. Decreased body weight gain and food consumption were present in dams at the highest dose during lactation. Decreased body weight gain compared to controls was observed in the offspring from dams in the high dose group. Liver discoloration occurred in offspring from the high dose group at LD 4 but was not present in animals examined after weaning. Similarly, in dose range finding studies in rats and follow-up mechanistic animal studies, the liver discoloration was observed and characterized as necrosis, fibrosis, and hemorrhage at equal to or greater than clinically relevant exposures based on AUC comparisons. The mechanistic studies further demonstrated the effect was likely attributable to vonoprazan exposure.
during lactation [see Use in Specific Populations (8.2)]. The clinical relevance of the liver findings is uncertain.

Exposure margins from vonoprazan between the animal and clinical studies for vonoprazan, amoxicillin and clarithromycin used in combination may be lower due to increased vonoprazan exposure from concomitant use with clarithromycin in patients [see Clinical Pharmacology (12.3)].

8.2 Lactation
Risk Summary

There are no data regarding the presence of vonoprazan in human milk, the effects on the breastfed infant, or the effects on milk production. Vonoprazan and its metabolites are present in rat milk. Liver injury occurred in offspring from pregnant and lactating rats administered oral vonoprazan at AUC exposures approximately equal to and greater than the MRHD [see Data]. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential risk of adverse liver effects shown in animal studies with vonoprazan, advise patients not to breastfeed during treatment with VOQUEZNA.

Data

Animal Data

In a PPND study in rats, in which the dams were administered oral vonoprazan during gestation and through lactation at up to 22-times the MRHD (based on AUC comparison), liver discoloration occurred in offspring from the high dose group [see Use in Specific Populations (8.1)].

Liver discoloration associated with necrosis, fibrosis, and hemorrhage in the offspring of dosed rats was also seen in dose-range finding studies and follow-up, mechanistic studies, including offspring in lactation only studies. These effects were reported in pups on LD 4 at doses from 3 to 100 mg/kg/day (approximately 0.2- to 22-fold the MRHD based on AUC values extrapolated from the PPND study) and on LD 14 at doses from 10 to 100 mg/kg/day dose groups (approximately 1- to 22-fold the MRHD based on an extrapolated AUC comparisons). In mechanistic studies, liver effects were observed in offspring treated only during lactation but not in offspring from animals only treated during gestation. In some of these studies, this finding was associated with increased offspring stomach weights that was reversed along with liver discoloration by concomitant treatment with a gastrointestinal prokinetic agent.

8.4 Pediatric Use

The safety and effectiveness of VOQUEZNA have not been established in pediatric patients.

8.5 Geriatric Use

There were 200 patients aged 65 years and older in the clinical trial for erosive esophagitis and relief of heartburn [see Clinical Studies (14.1)]. Of the total number of vonoprazan-treated patients there were 93 (18%) patients aged 65 years of age and older and 10 (2%) patients aged 75 years of age and older.

There were 218 patients aged 65 years and older in the clinical trial for the treatment of H. pylori infection [see Clinical Studies (14.3)]. Of the total number of vonoprazan-treated patients, there were 153 (22%) patients aged 65 years of age and older and 18 (3%) patients aged 75 years of age and older.

No overall differences in safety or effectiveness were observed between these patients and younger adult patients, and other reported clinical experience has not identified differences in responses between the geriatric and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

No clinically meaningful differences in the pharmacokinetics of vonoprazan are predicted in patients 65 years of age and older compared to younger adult patients [see Clinical Pharmacology (12.3)].

8.6 Renal Impairment

Healing of Erosive Esophagitis

No dosage adjustment of VOQUEZNA for the healing of erosive esophagitis is recommended in patients with mild to moderate renal impairment (eGFR 30 to 89 mL/min). Dosage reduction is recommended in patients with severe renal impairment (eGFR < 30 mL/min) [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

Maintenance of Healed Erosive Esophagitis

No dosage adjustment of VOQUEZNA for the maintenance of healed erosive esophagitis is recommended in patients with any degree of renal impairment.

Treatment of H. pylori infection

Use of VOQUEZNA is not recommended for the treatment of H. pylori infection in patients with severe renal impairment (eGFR < 30 mL/min) [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

Healing of Erosive Esophagitis

No dosage adjustment of VOQUEZNA for the healing of erosive esophagitis is recommended in patients with mild hepatic impairment (Child-Pugh A). Dosage reduction is recommended in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C) [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

Maintenance of Healed Erosive Esophagitis

No dosage adjustment of VOQUEZNA for the maintenance of healed erosive esophagitis is recommended in patients with any degree of hepatic impairment.

Treatment of H. pylori infection

Use of VOQUEZNA is not recommended for the treatment of H. pylori infection in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C) [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

11. DESCRIPTION

Vonoprazan (as the fumarate), is a potassium-competitive acid blocker. Chemically, it is 1H-pyrole-3-methanamine, 5-(2-fluorophenyl)-N-methyl-1-(3-pyridinylsulfonfonyl)-, (2E)-2-butenedioate (1:1). Its empirical formula is C$_{17}$H$_{16}$FN$_{3}$O$_{2}$S•C$_{4}$H$_{4}$O$_{4}$ with a molecular weight of 461.5. Vonoprazan fumarate has the following structure:

![Vonoprazan Structure](image)

Vonoprazan fumarate is white to nearly white crystals or crystalline powder which melts at 194.8°C. Vonoprazan fumarate is soluble in dimethyl sulfoxide; sparingly soluble in N,N-dimethylacetamide, slightly soluble in N,N-dimethylformamide, methanol and water; very slightly soluble in ethanol (99.5%); and practically insoluble in 2-propanol, acetone, 1-octanol, and acetonitrile.

VOQUEZNA (vonoprazan) tablets are available in two dosage strengths for oral administration: 10 mg of vonoprazan (equivalent to 13.36 mg of vonoprazan fumarate) and 20 mg of vonoprazan (equivalent to 26.72 mg of vonoprazan fumarate). Each film-coated tablet contains the following inactive ingredients: ascorbic acid, croscarmellose sodium, ferric oxide red (only in 20 mg tablets), ferric oxide yellow (only in 10 mg tablets), fumaric acid, hydroxypropyl cellulose, hypromellose, magnesium stearate, manitol, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism 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 pumps in a noncovalent and reversible manner.

12.2 Pharmacodynamics

Antisecretory Activity

Following a single 10 mg or 20 mg dose of vonoprazan, the onset of the antisecretory effect as measured by intragastric pH occurs within 2 to 3 hours. The elevated intragastric pH levels compared to placebo increase with dose and are maintained for over 24 hours after dosing. The inhibitory effect of vonoprazan on acid secretion increases with repeated daily dosing and steady state is achieved by Day 4. The antisecretory effect of vonoprazan decreases following drug discontinuation although intragastric pH remained elevated compared to placebo for 24 to 48 hours following the dose on Day 7.

The effects of vonoprazan 10 mg or 20 mg once daily for 7 days on 24-hour intragastric pH in healthy subjects are shown in Table 10.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VOQUEZNA 10 mg Once Daily</th>
<th>VOQUEZNA 20 mg Once Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Day 1</td>
<td>3.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Day 7</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>% Time Intragastric pH&lt;4 (hours)</td>
<td>6.8 (2h)</td>
<td>43.1 (10h)</td>
</tr>
<tr>
<td>% Time Intragastric pH&lt;6 (hours)</td>
<td>1.3 (1h)</td>
<td>20.7 (5h)</td>
</tr>
</tbody>
</table>

Cardiac Electrophysiology

At a single dose of 120 mg (6-times the maximum recommended dose), vonoprazan does not prolong the QT interval to any clinically relevant extent.

Severe Gastrin Effects

The effect of vonoprazan on serum gastrin concentrations was evaluated in 514 patients for up to 8 weeks (healing phase) and in 592 patients for up to 6 months (maintenance phase). During the healing phase, the mean fasting gastrin levels at Week 2 increased from baseline after treatment with VOQUEZNA 20 mg and levels were similar at Week 2 and Week 8. During the 6-month maintenance phase, the mean gastrin levels remained elevated with VOQUEZNA 10 mg and 20 mg and the mean serum gastrin levels returned to normal within 4 weeks of discontinuation of treatment. Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum CgA levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors [see Warnings and Precautions (8.8) and Drug Interactions (7)].
Enterochromaffin-Like Cell (ECL) Effects

Human gastric biopsy specimens were obtained from 135 patients treated with vonoprazan 10 mg or 20 mg once daily for up to 260 weeks. An increase in the incidence of hyperplasia of the parietal cells and G-cells was observed, which is consistent with the pharmacological action of a potassium-competitive acid blocker. No neoplastic changes were observed [see Nonclinical Toxicology (13.1), (13.2)].

12.3 Pharmacokinetics

Steady state pharmacokinetic (PK) parameters for vonoprazan 10 mg or 20 mg following once daily administration and vonoprazan 20 mg following twice daily administration from data collected across multiple studies are summarized in Table 11.

Table 11: Mean (%CV) Steady State Pharmacokinetic Parameters For Vonoprazan Following Once or Twice Daily Dosing

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Vonoprazan 10 mg</th>
<th>Vonoprazan 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Once Daily  (N=30)</td>
<td>Twice Daily  (N=32)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h) median (min, max)</td>
<td>1.5 (0.75, 3.0)</td>
<td>2.0 (0.75, 5.0)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>11.7 (27.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.1 (35.2)</td>
</tr>
<tr>
<td>AUC (hr*ng/mL)</td>
<td>92.9 (33.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>230.9 (41.3)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2z&lt;/sub&gt; (h)</td>
<td>7.7 (27.1)</td>
<td>7.9 (22.6)</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>120.2 (35.2)</td>
<td>100.2 (38.3)</td>
</tr>
<tr>
<td>V&lt;sub&gt;F&lt;/sub&gt; (L)</td>
<td>1270.7 (26.6)</td>
<td>1114.0 (39.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup> AUC<sub>24h</sub>

Once daily administration and vonoprazan 20 mg following twice daily administration from data collected across multiple studies are summarized in Table 11.

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Vonoprazan 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Twice Daily  (N=32)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h) median (min, max)</td>
<td>1.0 (1.0, 6.0)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>37.8 (36.1)</td>
</tr>
<tr>
<td>AUC (hr*ng/mL)</td>
<td>272.5 (30.5)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2z&lt;/sub&gt; (h)</td>
<td>6.8 (22.7)</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>81.3 (35.7)</td>
</tr>
<tr>
<td>V&lt;sub&gt;F&lt;/sub&gt; (L)</td>
<td>782.7 (34.4)</td>
</tr>
</tbody>
</table>

The pharmacokinetics of vonoprazan administered as a single 20 mg dose in patients with mild [Child-Pugh Class A (N=8)], moderate [Child-Pugh Class B (N=8)], or severe [Child-Pugh Class C (N=6)] hepatic impairment were compared to those with normal hepatic function (N=12). Compared to subjects with normal hepatic function, systemic exposure (AUC<sub>0-inf</sub>) of vonoprazan was 1.2-, 2.4-, and 2.6-times greater in patients with mild, moderate, and severe hepatic impairment, respectively [see Dosage and Administration (2.3)]. Protein binding of vonoprazan is not affected by impaired hepatic function.

Drug Interaction Studies

In Vitro Studies

Cytochrome P450 (CYP) Enzymes

In vitro studies have shown that vonoprazan directly and time-dependently inhibits CYP2C9, CYP2D6, and CYP3A4/5.

Transporter Systems

Vonoprazan inhibits multidrug and toxinn extrusion protein 1 (MATE1) and organic cation transporter 1 (OCT1), but only at concentrations higher than clinically relevant.

Clinical Studies

Combination Therapy with Vonoprazan, Amoxicillin, and Clarithromycin

When vonoprazan 20 mg, amoxicillin 750 mg and clarithromycin 400 mg were co-administered twice daily for 7 days (N=11), there was no effect on the pharmacokinetics of amoxicillin compared to amoxicillin alone. However, vonoprazan C<sub>max</sub> and AUC<sub>0-24h</sub> increased by 67% and 85%, respectively, and clarithromycin C<sub>max</sub> and AUC<sub>0-24h</sub> increased by 64% and 45%, respectively, compared to administration of each component alone.

Effect of Vonoprazan on CYP3A4 Substrates

When a single oral dose of midazolam 2 mg was administered following vonoprazan 20 mg twice daily for 7 days (N=20), midazolam AUC<sub>0-inf</sub> increased 93% compared to administration of midazolam alone.

Effect of CYP3A Inhibitors on Vonoprazan

When a single dose of 40 mg vonoprazan (twice the maximum recommended dose) was administered with clarithromycin 500 mg twice daily for 7 days (N=16), vonoprazan AUC<sub>0-inf</sub> increased 58% compared to administration of vonoprazan alone.

CDAD induction by CYP3A4 inhibitors or low dose aspirin

When a single dose of 40 mg vonoprazan (twice the maximum recommended dose) was co-administered with diclofenac 25 mg, meloxicam 10 mg, or aspirin 190 mg, there were no clinically meaningful changes in exposure of vonoprazan, diclofenac, meloxicam, or aspirin compared to administration of each drug alone.

Model-Informed Approaches

Effect of CYP3A Inducers on Vonoprazan

Vonoprazan exposures are predicted to be 80% lower when co-administered with a strong CYP3A4 inducer such as rifampicin and 50% lower when co-administered with a moderate CYP3A4 inducer such as efavirenz.

12.4 Microbiology

Antimicrobial Activity

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of H. pylori infection [see Clinical Studies (14.3)]. The following in vitro data are available, but their clinical significance is unknown. Clarithromycin and amoxicillin are active in vitro against most isolates of H. pylori.

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

In a 24-month carcinogenicity study in mice, vonoprazan at daily oral doses of 6, 20, 60, and 200 mg/kg/day (approximately 0.4-, 4-, 19-, and 93-times the MRHD based on AUC) produced hyperplasia of neuroendocrine cells, gastroat and benign and/or malignant neuroendocrine cell tumors (carcinoids) in the stomach at all doses in males and at 60 mg/kg/day and greater in females. In liver, increased incidences of hepatocellular adenomas and carcinomas were observed at doses of 20 mg/kg/day and greater in males and 60 mg/kg/day and greater in females.

In a 24-month carcinogenicity study in Sprague-Dawley rats, vonoprazan at daily oral doses of 5, 15, 50, and 150 mg/kg/day (approximately 0.6-, 4-, 19-, and 65-times the MRHD based on AUC) produced benign and/or malignant neuroendocrine cell tumors in the stomach in both male and female rats at doses of 5 mg/kg/day or more. Increased incidence of hepatocellular adenoma and carcinomas and hepatocellular carcinomas were observed at doses of 50 and 150 mg/kg/day.

In both mice and rats, neuroendocrine tumors in the stomach occurred in association with neuroendocrine hyperplasia and gasstrophy in the stomach and increased plasma gastrin concentrations that are consistent with inhibition of gastric acid secretion. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with proton pump inhibitors or high doses of H<sub>2</sub>-receptor antagonists.
14.1 Healing of Erosive Esophagitis and Relief of Heartburn
The effectiveness and safety of VOQUEZNA was evaluated in a randomized, active-controlled, double-blind, eight-week study conducted in the United States and in 1024 adult patients with endoscopically confirmed erosive esophagitis (NCT04124926). Severity of the disease was classified based on the Los Angeles (LA) Classification Grading System (Grades A through D). Patients were randomized to one of the following treatment groups: VOQUEZNA 20 mg once daily or lansoprazole 30 mg once daily 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. Based on the LA Classification, 66% of patients had mild erosive esophagitis (Grades A or B) and 34% of patients 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 years); 53% were female; 12% identified as Hispanic or Latino; 91% identified as White, 6% as Black or African American, and 3% identified as another racial group. Healing of erosive esophagitis was assessed at Week 2 and Week 8 and resolution of heartburn symptoms was evaluated 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.

Healing of All Grades of Erosive Esophagitis
The primary endpoint, was endoscopically confirmed complete healing of all grades of erosive esophagitis at Week 2 or Week 8, as shown in Table 12.

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Treatment Group</th>
<th>VOQUEZNA 20 mg Once Daily N=514 %</th>
<th>Lansoprazole 30 mg Once Daily N=510 %</th>
<th>Treatment Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2 or 8</td>
<td>93</td>
<td>85</td>
<td>8% (4.5, 12.2)</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>74</td>
<td>68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Demonstrated noninferiority to Lansoprazole.

Healing of Erosive Esophagitis in Subgroups with LA Grade C or D Esophagitis
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, 70% of 177 VOQUEZNA treated patients and 53% of 174 lansoprazole treated patients achieved healing (18% treatment difference; 95% CI 7.4, 27.4).

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.

Relief of Heartburn in Patients with Erosive Esophagitis During the Healing Phase
The percentage of 24-hour heartburn-free days through Week 8 was evaluated as a secondary endpoint and results are shown in Table 13.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VOQUEZNA 20 mg Once Daily N=514 %</th>
<th>Lansoprazole 30 mg Once Daily N=510 %</th>
<th>Treatment Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>67 ± 35</td>
<td>64 ± 35</td>
<td>3% (-1.6, 7.0)</td>
</tr>
<tr>
<td>Median</td>
<td>81</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

*a Demonstrated noninferiority to Lansoprazole.

Other Healing of Erosive Esophagitis Studies
Two additional randomized, active-controlled, double-blind studies conducted outside of the United States, of similar design to the United States trial, also demonstrated non-inferiority of vonoprazan 20 mg once daily compared to lansoprazole 30 mg once daily for the primary endpoint of healing of all grades of erosive esophagitis by Week 8.

14.2 Maintenance of Healed Erosive Esophagitis and Relief of Heartburn
Patients who completed the healing phase of the erosive esophagitis study (NCT04124926) and showed endoscopically confirmed healed erosive esophagitis at Week 2 or Week 8 were re-randomized in the maintenance phase 1:1:1 to either VOQUEZNA 10 mg once daily, a higher dosage of VOQUEZNA, or lansoprazole 15 mg once daily. Maintenance of healing and resolution of heartburn symptoms were evaluated over 24 weeks. The higher VOQUEZNA dose group did not demonstrate additional treatment benefit compared to VOQUEZNA 10 mg once daily.

Maintenance of Healed Erosive Esophagitis
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.

The maintenance rates of healed erosive esophagitis are shown in Table 14.

Table 14: Maintenance Rates of Healed Erosive Esophagitis in Adults through Week 24

<table>
<thead>
<tr>
<th>Baseline Severity</th>
<th>Treatment Group</th>
<th>VOQUEZNA 10 mg Once Daily N=293 %</th>
<th>Lansoprazole 15 mg Once Daily N=294 %</th>
<th>Treatment Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All LA Grades:</td>
<td>Week 24</td>
<td>79%</td>
<td>72%</td>
<td>7% (0.2, 14.1)</td>
</tr>
<tr>
<td>LA Grade C or D:</td>
<td>Week 24</td>
<td>75%</td>
<td>61%</td>
<td>13% (0.02, 26.1)</td>
</tr>
</tbody>
</table>

*a Demonstrated non-inferiority to Lansoprazole.

*b Demonstrated superiority to Lansoprazole.

Relief of Heartburn During Maintenance of Healed Erosive Esophagitis
The percentage of 24-hour heartburn-free days through Week 24 was evaluated for non-inferiority as a secondary endpoint as shown in Table 15.

Table 15: Percentage of 24-Hour Heartburn-Free Days through Week 24

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Group</th>
<th>VOQUEZNA 10 mg Once Daily N=293 %</th>
<th>Lansoprazole 15 mg Once Daily N=294 %</th>
<th>Treatment Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>81 ± 29</td>
<td>79 ± 27</td>
<td>2% (-2.3, 6.8)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>95</td>
<td>89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Demonstrated non-inferiority to Lansoprazole.

Other Maintenance of Healed Erosive Esophagitis Studies
Two additional randomized, active-controlled, double-blind studies conducted outside of the United States, of similar design to the United States trial, also demonstrated non-inferiority of vonoprazan 10 mg once daily compared to lansoprazole 15 mg once daily for the primary endpoint of maintenance of healed erosive esophagitis (all grades) through Week 24.

14.3 Treatment of Helicobacter pylori Infection
The effectiveness and safety of VOQUEZNA, amoxicillin and clarithromycin (triple therapy) and VOQUEZNA and amoxicillin (dual therapy) were evaluated in a randomized, controlled, double-blind (triple therapy)/open-label (dual therapy) study conducted in the United States and Europe in treatment-naive 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 (NCT04167670). Patients were randomized 1:1:1 to one of the following regimens administered for 14 consecutive days:

- VOQUEZNA 20 mg twice daily plus, amoxicillin 1,000 mg twice daily, and clarithromycin 500 mg twice daily
- VOQUEZNA 20 mg twice daily and amoxicillin 1,000 mg three times daily
- Lansoprazole 30 mg twice daily, amoxicillin 1,000 mg twice daily, and clarithromycin 500 mg twice daily

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 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.

A total of 346 patients received VOQUEZNA, amoxicillin, and clarithromycin, 348 patients received VOQUEZNA and amoxicillin, and 345 patients received Lansoprazole, amoxicillin, and clarithromycin. These patients had a mean age of 51 years (range 20 to 67 years);
62% were female; 27% identified as Hispanic or Latino; 89% identified as White, 7% as Black or African American, 2% as Asian, and 2% identified as another racial group.

VOQUEZNA, amoxicillin, and clarithromycin and VOQUEZNA and amoxicillin were shown to be noninferior 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 shown in Table 16.

### Table 16: Eradication Rates of H. pylori in Adult Patients at least 27 Days Post-Therapy - mITT

<table>
<thead>
<tr>
<th>VOQUEZNA Amoxicillin, and Clarithromycin</th>
<th>VOQUEZNA and Amoxicillin</th>
<th>Lansoprazole, Amoxicillin, and Clarithromycin (LAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with H. pylori infection who did not have a clarithromycin or amoxicillin resistant strain at baseline</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>Treatment Difference from LAC (95% CI)</td>
<td>85 (222)</td>
<td>79 (208)</td>
</tr>
<tr>
<td>Treatment Difference from LAC (95% CI)</td>
<td>(-0.8, 12.6)</td>
<td>(-7.4, 6.8)</td>
</tr>
<tr>
<td>All randomized patients with H. pylori infection at baseline</td>
<td>81 (273)</td>
<td>77 (250)</td>
</tr>
<tr>
<td>Treatment Difference from LAC (95% CI)</td>
<td>12 (5.7, 18.8)</td>
<td>9 (1.9, 15.4)</td>
</tr>
</tbody>
</table>

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.

### Important Administration Instructions

- **VOQUEZNA can be taken with or without food [see Dosage and Administration (2) and Clinical Pharmacology (12.3)].**
- **Swallow VOQUEZNA tablets whole; do not chew or crush the tablet.**
- **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 take your next dose at your regularly scheduled time [see Dosage and Administration (2)].
  - 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 your next dose at the regularly scheduled time. Continue the normal dosing schedule until the treatment is completed [see Dosage and Administration (2)].

VOQUEZNA is manufactured for and distributed by Phathom Pharmaceuticals, Inc.

### Lactation

To not breastfeed during treatment with VOQUEZNA [see Use in Specific Populations (8.2)].

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VOQ222 V1

### PATIENT INFORMATION

**VOQUEZNA® (voo kweez nah) (vonoprazan) tablets, for oral use**

**What is VOQUEZNA?**

VOQUEZNA is a prescription medicine called a potassium-competitive acid blocker. VOQUEZNA reduces the amount of acid in your stomach.

**VOQUEZNA is used in adults:**

- for 8 weeks to heal acid-related damage to the lining of the esophagus (called erosive esophagitis) and for relief of heartburn related to erosive esophagitis.
- for up to 6 months to maintain healing of erosive esophagitis and for relief of heartburn related to erosive esophagitis.
- for 14 days with the antibiotics amoxicillin and clarithromycin to treat an infection caused by bacteria called Helicobacter pylori (H. pylori).
- for 14 days with the antibiotic amoxicillin to treat an infection caused by bacteria called H. pylori.

It is not known if VOQUEZNA is safe and effective in children.

**Do not take VOQUEZNA if you are:**

- allergic to vonoprazan or any of the ingredients in VOQUEZNA.

See the end of this Patient Information leaflet for a complete list of ingredients in VOQUEZNA. Allergic reaction symptoms may include trouble breathing, rash, itching and swelling of your face, lips, tongue, or throat.

- taking a medicine that contains rilpivirine (EDURANT, COMPLERA, JULUCA, ODEFSY, CABENUVA) used to treat HIV-1 (Human Immunodeficiency Virus).

Before taking VOQUEZNA, tell your healthcare provider about all of your medical conditions, including if you:

- have low magnesium, calcium, or potassium in your blood or you are taking a medicine to increase urine (diuretic).
• have kidney problems.
• have liver problems.
• are pregnant, think you may be pregnant or plan to become pregnant. It is not known if VOQUEZNA will harm your unborn baby. Call the Phathom Pharmaceuticals, Inc. Adverse Event reporting line at 1-888-775-7428 if you become pregnant while taking VOQUEZNA.
• are breastfeeding or plan to breastfeed. It is not known if VOQUEZNA passes into your breast milk. You and your healthcare provider should decide if you will take VOQUEZNA or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine. VOQUEZNA may affect how other medicines work, and other medicines may affect how VOQUEZNA works.

How should I take VOQUEZNA?
• Take VOQUEZNA exactly as your healthcare provider tells you to take it.
• Do not change your dose or stop taking VOQUEZNA without talking to your healthcare provider first.
• Take VOQUEZNA with or without food.
• Swallow VOQUEZNA tablets whole. Do not chew or crush the tablet.
• For the treatment of erosive esophagitis:
  ○ If you miss a dose of VOQUEZNA, take it as soon as possible within 12 hours after the missed dose. If more than 12 hours have passed, skip the missed dose and take the next dose at the regularly scheduled time.
• For the treatment of H. pylori infection:
  ○ If you miss a dose of VOQUEZNA, take it as soon as possible within 4 hours after the missed dose. If more than 4 hours have passed, skip the missed dose and take the next dose at the regularly scheduled time. Continue your regular dosing schedule until the treatment is completed.

What are the possible side effects of VOQUEZNA?
VOQUEZNA may cause serious side effects, including:
• A type of kidney problem (acute tubulointerstitial nephritis). Some people who take VOQUEZNA may develop a kidney problem called acute tubulointerstitial nephritis. Call your healthcare provider right away if you have a decrease in the amount that you urinate or if you have blood in your urine.
• Diarrhea caused by an infection (Clostridoides difficile) in your intestines. Call your healthcare provider right away if you have watery stools, stomach pain, or fever that does not go away.
• Bone fractures (hip, wrist, or spine). Bone fractures in the hip, wrist, or spine may happen in people who take multiple daily doses of another type of medicine that reduces acid in your stomach known as proton pump inhibitors (PPI medicines) for a long period of time (a year or longer). Tell your healthcare provider if you have a bone fracture, especially in the hip, wrist, or spine.
• Severe skin reactions. VOQUEZNA can cause rare but severe skin reactions that may affect any part of your body. These serious skin reactions may need to be treated in a hospital and may be life threatening:
  ○ Skin rash which may have blistering, peeling or bleeding on any part of your skin (including your lips, eyes, mouth, nose, genital, hands or feet).
  ○ You may also have fever, chills, body aches, shortness of breath, or enlarged lymph nodes.
If you have any of these symptoms, stop taking VOQUEZNA and call your healthcare provider right away. These symptoms may be the first sign of a severe skin reaction.
• Low Vitamin B-12 levels. VOQUEZNA lowers the amount of acid in your stomach. Stomach acid is needed to absorb Vitamin B12 properly. Tell your healthcare provider if you have symptoms of low vitamin B12 levels, including irregular heartbeat, shortness of breath, lightheadedness, tingling or numbness in the arms and legs, muscle weakness, pale skin, feeling tired, or mood changes. Talk with your healthcare provider about the risk of low Vitamin B12 levels if you have been on VOQUEZNA for a long time.
• Low magnesium levels in the body can happen in people who take VOQUEZNA. Tell your healthcare provider right away if you have symptoms of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, or spasms of hands, feet, or voice.
• Stomach growths (fundic gland polyps). A certain type of stomach growth called fundic gland polyps may happen in people who take VOQUEZNA for a long time (more than a year). Talk with your healthcare provider about the risk of fundic gland polyps if you have been on VOQUEZNA for a long time.

The most common side effects of VOQUEZNA for treatment of erosive esophagitis include:
• stomach inflammation
• diarrhea
• stomach bloating
• stomach pain
• nausea
• indigestion
• high blood pressure
• urinary tract infection

The most common side effects of VOQUEZNA when used with antibiotics for treatment of H. pylori infection include:
• diarrhea
• temporary changes in sense of taste
• vaginal yeast infection
• stomach pain
• headache
• high blood pressure
• cold-like symptoms
These are not all the possible side effects of VOQUEZNA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VOQUEZNA?
• Store VOQUEZNA at room temperature between 68°F to 77°F (20°C to 25°C).

General information about the safe and effective use of VOQUEZNA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VOQUEZNA for a condition for which it was not prescribed. Do not give VOQUEZNA to other people, even if they have the same symptoms you have. It may harm them.
You can ask your healthcare provider or pharmacist for information about VOQUEZNA that is written for health professionals.

What are the ingredients of VOQUEZNA?
Active ingredient: vonoprazan
Inactive ingredients: ascorbic acid, croscarmellose sodium, ferric oxide red (only in 20 mg tablets), ferric oxide yellow (only in 10 mg tablets), fumaric acid, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

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