

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215151Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24**

Date: October 31, 2023

Reviewer: Joel L. Weissfeld, MD MPH
Division of Epidemiology 1

Team Leader: Benjamin J. Booth, PhD MS
Division of Epidemiology 1

Division Director: Wei Hua, MD PhD MS MHS
Division of Epidemiology 1

Subject: ARIA Sufficiency Memo (Expedited Template for Pregnancy Safety)

Drug Name(s): vonoprazan (VOQUEZNA®)

Application Type/Number: NDA 215151

Applicant/sponsor: Phathom Pharmaceuticals

OSE TTT #: 2023-6444

1. BACKGROUND INFORMATION

1.1. Medical Product

Vonoprazan (VOQUEZNA®) NDA 215151 seeks FDA approval for erosive esophagitis in adults. Vonoprazan, a small molecule (molecular weight 461.5), is a potassium-competitive acid blocker (P-CAB), which suppresses basal and stimulated gastric acid secretion at the secretory surface of gastric parietal cells. Draft labeling recommends vonoprazan for oral ingestion once daily, 20 mg for 8 week and 10 mg for ≤6 months to heal erosive esophagitis and maintain healing, respectively. Vonoprazan has a mean terminal elimination half-life of ≈8 hours.

If combined with (1) amoxicillin and clarithromycin (NDA 215152) or (2) amoxicillin alone (NDA 215153), vonoprazan may be used to treat *Helicobacter pylori* infection in adults.^a

1.2. Describe the Safety Concern

Vonoprazan is the first-in-class of potassium-competitive acid blocking agents. Despite the lack of a safety signal in animal reproductive toxicology studies for vonoprazan monotherapy, the lack of sufficient human data with vonoprazan exposure in pregnancy is a safety issue.

Vonoprazan is anticipated to be used in females of reproductive potential, wherein exposure to the drug may occur before the female is aware of the pregnancy. Data are needed on the safe use of vonoprazan-containing products during pregnancy as there is currently no available human data to inform the safety of vonoprazan combination products during pregnancy, and the small number of pharmacovigilance reports on pregnancy exposure to vonoprazan monotherapy are missing information to assess for a causal relationship between the drug and maternal/fetal outcomes.

As presented in draft vonoprazan labeling (Section 8.1),^b pre-clinical studies in:

- Pregnant rats showed (1) fetal abnormalities (e.g., ventricle septal defect, mal-positioned subclavian artery, tail abnormality, and small anal opening) at maternal exposures equal to 130-times the equivalent maximum recommended human dose (MRHD) and (2) no fetal abnormality at maternal exposures equal to 27-times MRHD.
- Pregnant rabbits showed abortion and decreased body weight but no fetal developmental toxicity at maternal exposures equal to 10-times MRHD.
- Rats showed decreased maternal and offspring body weight gain at maternal exposures (gestation day 6 through lactation day 20) equal to 22-times but not 1.1-times MRHD.

The clinical safety database for NDA 215151 identified five reports of pregnancy in women treated with vonoprazan during the first trimester, specifically,^c

- Miscarriage in a subject ((b) (6)) 1 month after completing food effects Study TAK-438-109.
- Normal birth in a subject ((b) (6)) with a negative pregnancy test after completing 12 days of dosing in duodenal ulcer Study TAK-438/CCT-102.^d

^a NDAs approved on May 3, 2022, by the Division of Anti-Infectives (DAI).

^b United States Prescribing Information for VOQUEZNA™ TRIPLE PAK™ and VOQUEZNA™ DUAL PAK™, Revised: 8/2023, accessed at Drugs@FDA on October 19, 2023.

^c Summary of Clinical Safety, Module 2.7.4, submitted to NDA 21515 (eCTD 0002) on March 11, 2022.

^d Pregnancy reported by subject approximately 6 months after study completion.



- Normal birth in a subject ((b) (6)) with positive pregnancy test after 344 days of dosing in peptic ulcer Study TAK-438/OCT-301.
- Elective abortion in a subject ((b) (6)) with a positive pregnancy test after 28 days of dosing in duodenal ulcer Study TAK-438_304.
- Unknown outcome in a subject ((b) (6)) with a positive pregnancy test after 76 days of maintenance dosing in erosive esophagitis Study EE-301.

After the Division of Epidemiology II deemed **ARIA NOT SUFFICIENT** for the *H. pylori* indication, DAI required (in 2022; under FDAAA Section 505(o)(3)) two post-approval pregnancy studies (PMRs 4270-1 and 4270-2).^e Upon review of NDA 215151, the Division of Pediatrics and Maternal Health (DPMH) determined that protocols addressing these PMRs should “add patients with erosive esophagitis who become pregnant during treatment with Voquezna [sic].”^f This ARIA Memorandum addresses ARIA sufficiency for the erosive esophagitis indication.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an “X” in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- No approved indication, but use in women of child-bearing age is a general concern

2.2. Regulatory Goal

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

^e Day H, N Pratt, and M Falconer, Epidemiology ARIA Sufficiency Memorandum, filed under NDAs 215152 and 215153 on April 27, 2022 (DARRTS Reference ID: 4974823).

^f Liedtka J, T Johnson, and LP Yao, Division of Pediatric and Maternal Health Memorandum, filed under NDA 215151 on October 24, 2022 (DARRTS Reference ID: 5063152).

**2.3. What type of analysis or study design is being considered or requested along with ARIA?
Check all that apply.**

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify: Alternative study designs would be considered: e.g., a retrospective cohort study using claims or electronic medical record data or a case control study

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- Study Population
- Exposures (pregnancy registry)
- Outcomes (pregnancy registry)
- Covariates (pregnancy registry)
- Analytical Tools (additional pregnancy study)

For any checked boxes above, please describe briefly:

The Division of Epidemiology I (DEPI) considered PMR requests for two separate studies: (1) a pregnancy registry and (2) an additional pregnancy study.

DEPI found **ARIA NOT SUFFICIENT** for the pregnancy registry. (See Section 2.5, below, for a description of the pregnancy registry.) DEPI disqualified ARIA in three assessment domains (Exposures, Outcomes, and Covariates) for reasons summarized below.

- Exposures and Outcomes: ARIA precludes data collection sources and methods considered essential. Pregnancy registries collect and assemble detailed patient information from sources that include direct patient report and physician questionnaire. Specifically, patient registries require complete and accurate information about (1) teratogenic and non-teratogenic drug exposures (e.g., precise timing of specific exposures in relation to days before or after pregnancy onset) and (2) clinically specific outcomes (e.g., type of congenital malformation). A requirement for accurate classification of congenital malformation outcomes necessitates independent review of primary source documents by physicians with special training or expertise in clinical genetics or birth defects.
- Covariates: Data sources processed by ARIA inaccurately and incompletely capture certain covariates considered critical (e.g., smoking, folate supplementation, and family history of birth defects).

The following text summarizes the procedure DEPI used to decide on **ARIA SUFFICIENCY** for an additional study that fits the following description.

An additional pregnancy study that uses a different design from the Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case



control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to vonoprazan-containing products during pregnancy compared to an unexposed control population.

On October 26, 2023, DEPI analysts met in conference with clinical experts from the Division of Gastroenterology (DG) and DPMH to obtain better understanding of the regulatory purpose, goals, and clinical rationale behind the request for a second pregnancy study in addition to a pregnancy registry. On October 27, DPMH responded in writing by stating that the study should (1) “evaluate the safety of vonoprazan-containing products in females exposed during pregnancy, including assessing risks of pregnancy complications, major congenital malformations, and other adverse effects on the developing fetus and neonate,” (2) “provide data regarding rare pregnancy outcomes,” and (3) “corroborate findings from the pregnancy registry.”

As summarized in the following table, a DEPI analyst (JLW) judged ARIA capabilities in five assessment domains in relation to the stated regulatory purpose and goals for the additional pregnancy study. In summary, the DEPI analyst identified four ARIA cautions but no ARIA disqualifications. After balancing (1) uncertainties introduced by restricted ARIA capabilities, (2) generalized interest in detecting vonoprazan-associated signals of possible reproductive harm, and (3) specific interest on rare outcomes, this analyst recommended that DEPI deem **ARIA SUFFICIENT** for an additional pregnancy study.

ASSESSMENT DOMAIN	QUALITATIVE JUDGMENT OF ARIA CAPABILITIES	COMMENTS
Study Population	Possibly supported	ICD-10 classifies erosive esophagitis (EE) under a clinically non-specific code (ICD-10 K20.8 Other esophagitis). ARIA identifies pregnancy with acceptable accuracy.
Exposures	Possibly supported	National Drug Codes (NDCs) permit identification of pharmacy dispensings for vonoprazan and comparators (proton pump inhibitors). ARIA approximates pregnancy start and end dates. ARIA approximates start dates with greater uncertainty for pregnancies with non-livebirth than livebirth outcome. Variation between pharmacy prescription and patient behavior introduces uncertainty in timing of exposure in relation to pregnancy.
Outcomes	Possibly supported	Diagnosis codes and code combinations measure livebirth and non-livebirth outcomes with error acceptable for some but not all applications. Acceptably accurate identification of Major Congenital Malformation (MCM) requires linkages between maternal and infant records. Pregnancies excluded because of missing linked infant not only reduces sample size but also introduces potential for selection bias.
Covariates	Supported	ARIA poorly captures certain covariates (e.g., social factors, behavioral factors, and reproductive history) strongly associated with adverse pregnancy outcome.



		ARIA design and statistical controls, however, adequately support signal detection applications.
Analytical Tools	Possibly supported	Investigating both livebirth and non-livebirth outcomes complicates analysis because ARIA uses one method to identify pregnancies at risk for livebirth outcomes (e.g., MCM) and a different method to identify pregnancies at risk for non-livebirth outcomes (e.g., spontaneous abortion).

On October 30, 2023, DEPI hosted a cross-office Signal Assessment Meeting (SAM) to agree on PMR goals, discuss ARIA capabilities, and decide **ARIA SUFFICIENCY**. The SAM recognized both livebirth (e.g., MCM) and non-livebirth outcomes (i.e., spontaneous abortion and stillbirth) as critical elements for postmarket assessment. The SAM learned that Sentinel capabilities for assessing non-livebirth outcomes have not been qualified for use under ARIA. In addition, ARIA lacks access to medical records. Although the study using claims or electronic medical data may be algorithm-based for signal detection, if an imbalance is shown in any of the outcomes being investigated, outcome validation or a chart-confirmed analysis is desirable. Based on these considerations, the SAM concluded with consensus findings of **ARIA NOT SUFFICIENT** for a prospective pregnancy registry and **ARIA NOT SUFFICIENT** for an additional pregnancy study that uses a different design.

2.5. Please include the proposed PMR language in the approval letter.

On October 17, 2023, the Applicant (NDA 215151, eCTD 0039) agreed to include patients with erosive esophagitis in two studies described as follows.

PMR #1

Conduct a prospective, registry based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to vonoprazan-containing products during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR #2

An additional pregnancy study that uses a different design from the Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to vonoprazan-containing products during pregnancy compared to an unexposed control population.

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/s/

JOEL L WEISSFELD
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JUDITH W ZANDER
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SARAH K DUTCHER
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: October 26, 2023

To: Maureen Dewey, MPH, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology (DG)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Concurrence with Submitted: Patient Package Insert
(PPI)

Drug Name (established name): VOQUEZNA (vonoprazan)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 215151

Applicant: Phathom Pharmaceuticals, Inc.

1 INTRODUCTION

On May 19, 2023, Phathom Pharmaceuticals, Inc. submitted for the Agency's review a Resubmission to the original New Drug Application (NDA) for VOQUEZNA (vonoprazan) tablets, for oral use (NDA 215151). This submission provides a response to the FDA Complete Response Letter (CRL) dated February 7, 2023, and as described by the Applicant:

This resubmission is in alignment with the discussion at the Type A meeting held 07 March 2023, to discuss the CRL and the regulatory pathway for submission of a reformulation of vonoprazan tablets [REDACTED] (b) (4)

The proposed indication for VOQUEZNA (vonoprazan) tablets, for oral use is for the:

- Healing of all grades of erosive esophagitis and relief of heartburn.
- Maintenance of healing of all grades of erosive esophagitis and relief of heartburn.
- Treatment of *Helicobacter pylori* (*H. pylori*) infection.

On June 5, 2023, the Division of Gastroenterology (DG) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for VOQUEZNA (vonoprazan) tablets, for oral use.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed PPI for VOQUEZNA (vonoprazan) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft VOQUEZNA (vonoprazan) tablets, for oral use PPI received on May 19, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on October 19, 2023.
- Draft VOQUEZNA (vonoprazan) tablets, for oral use Prescribing Information (PI) received on May 19, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on October 19, 2023.
- Patient Labeling Review for VOQUEZNA (vonoprazan) tablets, for oral use dated December 22, 2022.

3 CONCLUSIONS

We find the Applicant's proposed PPI is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 26, 2023

To: Maureen Dewey, Project Manager, DG

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for **VOQUEZNA (vonoprazan) tablets, for oral use**

NDA: 215151

In response to DG's consult request dated May 30, 2023, OPDP has reviewed the proposed product labeling (PI) and Patient Package Insert (PPI) for Voquezna.

Labeling: OPDP has no comments on the proposed labeling based on the draft PI or PPI received by electronic mail from DG on October 25, 2023.

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
10/26/2023 10:16:00 AM

Consult

Requesting Division: Division of Gastroenterology

Date requested: May 18, 2023

Desired completion date: August 30, 2023

Drug: Vonoprazan

Sponsor: Phathom Pharmaceuticals, Inc.

Medical Officer: Mayurika Ghosh, MD, Division of Anti-Infectives (DAI)

Executive summary

The Division of Gastroenterology (DG) requests a consult to advise on any safety labeling changes to the draft label for vonoprazan in healing of erosive esophagitis (EE) and maintenance of healing of EE (NDA 215151 under review) based on two clinical study reports from two *H. pylori* trials for quadruple therapy containing vonoprazan. A review of the study reports does not identify any new signals. Hypersensitivity reactions, rash in patients with mononucleosis as well as several Warnings and Precautions due to the clarithromycin component, i.e., QT prolongation, hepatotoxicity, serious adverse reactions due to concomitant use with other drugs, embryo-fetal toxicity, myasthenia gravis are noted in the VOQUEZNA triple Pak and dual Pak approved prescribing information (PI) for the treatment of *H. pylori*. This medical officer (MO) recommends cross-referencing this information using the following language at the end of (b) (4) section of the NDA 215151 PI “For information about (b) (4) of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with VOQUEZNA, refer to the (b) (4) section of the corresponding prescribing information.” (b) (4), (b) (5)

Background

New Drug Application (NDA) 215151 for VOQUEZNA (Vonoprazan tablets 10 mg and 20 mg) submitted on March 11, 2022, for the indication of healing and maintenance of healing of all grades of erosive esophagitis and relief of heartburn, received a Complete Response on February 7, 2023. The Applicant resubmitted the NDA on May 19, 2023, with a reformulation of vonoprazan tablets (b) (4). Of note, NDAs 215152 VOQUEZNA Triple Pak (vonoprazan tablets, amoxicillin capsules, and clarithromycin tablets)/215153 VOQUEZNA Dual Pak (vonoprazan tablets and amoxicillin capsules) approved on May 3, 2022, for the treatment of *H. pylori* infection, are not marketed. The primary support for approval of these applications is from

study HP-301, a three-arm study comparing vonoprazan triple therapy and vonoprazan dual therapy with lansoprazole triple therapy (with clarithromycin and amoxicillin).

NDA 215151 submission includes study reports from the two trials for quadruple therapy for *H. pylori*, conducted in China inclusive of the safety data (i.e., case reports for deaths/discontinuations). DG requests a summary of the new safety data for NDA review including any recommendations for labeling.

Vonoprazan is a potassium-competitive acid blocker that suppresses gastric acid secretion, and amoxicillin and clarithromycin are components of other approved combination therapies for the treatment of *H. pylori* infection. The safety profile of the vonoprazan-containing regimens studied is generally similar to that of currently approved proton pump inhibitor/antimicrobial drug combinations for the treatment of *H. pylori* infection. The most common adverse reactions reported in subjects treated with a vonoprazan-containing regimen are diarrhea, dysgeusia, abdominal pain, headache, and vulvovaginal candidiasis.

Clinical studies for *H.pylori* (China)

The two trials for quadruple therapy for *H. pylori* include a phase 1 double blind, parallel group safety, tolerability, and pharmacokinetic study (Vonoprazan-1001) comparing vonoprazan and esomeprazole, both in combination with bismuth, clarithromycin, and amoxicillin, and a phase 3, randomized double blind efficacy and safety study (Vonoprazan-3002) comparing quadruple therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg BID) with vonoprazan 20 mg twice daily versus quadruple therapy with esomeprazole 20 mg twice daily for 14 days.

In study (Vonoprazan-1001), there were 22 subjects in both the vonoprazan and esomeprazole groups. The mean exposure to the study drugs was 13.5 days and similar in both groups. There were no deaths or SAEs in the study. There was a lower frequency of TEAEs leading to study drug discontinuation in the vonoprazan group compared to the esomeprazole group (9% versus 23%). The TEAEs leading to study drug discontinuation were increased ALT and AST, noted in two subjects in the vonoprazan group and four subjects in the esomeprazole group. The increase in ALT and AST were moderate in intensity for two subjects (1 in each treatment group) and mild in intensity for all other subjects, with complete recovery. The overall incidence of TEAEs was 96% in both study groups and mostly mild. The most frequently reported vonoprazan related TEAEs were dysgeusia (lower frequency in the vonoprazan group compared to esomeprazole; 68% versus 82%) and increased ALT and increased AST (lower frequency in the esomeprazole group 40% versus 35%). There was no clinically significant hematology, chemistry values noted in the vonoprazan group. One subject in the vonoprazan group experienced markedly prolonged QT intervals (≥ 460 ms) before dosing on Day 3, Day 7, and Day 14, however these results were not clinically significant. There were no bismuth-related neurological AEs. Overall, these results showed that safety and tolerability were comparable between the two study groups. Vonoprazan had no significant effect on plasma bismuth exposure and the drug-interaction potential and tolerability with quadruple therapy with bismuth,

clarithromycin, amoxicillin, and vonoprazan were comparable to those of quadruple therapy with esomeprazole.

In the phase 3 vonoprazan-3002 trial, 256 subjects were randomized to the vonoprazan group and 254 subjects to the esomeprazole group. The study included 62% females with mean age of 39 years. The study met non inferiority of the vonoprazan-based quadruple therapy (86.8%) compared with esomeprazole-based quadruple therapy (86.7%) with a primary efficacy endpoint of *H. pylori* eradication rate at week four posttreatment. Mean (SD) study drug exposure was 13.9 days. The overall incidence of TEAEs was 69% in the vonoprazan group and the TEAE were mostly mild to moderate in intensity. The most frequent TEAE was dysgeusia, reported in 32.4% of subjects in the vonoprazan group. The incidence of drug related TEAEs was 38% in the vonoprazan group. Within the hepatobiliary disorders System Organ Class, the incidence of drug related TEAEs was 6.6% in the vonoprazan group (17 subjects with the PT hepatic function abnormal) compared to 3.1% in the esomeprazole group (8 subjects with the PT hepatic function abnormal).

There were three serious adverse events (SAEs) in the vonoprazan group. The SAEs related to vonoprazan group was supraventricular arrhythmia in a 61-year-old male who developed paroxysmal atrial fibrillation one day after completion of a 14-day course of treatment. The event treated with ablation and anticoagulation resolved and the echocardiogram did not reveal any structural disease. The drug related TEAEs resulting in study drug discontinuation were abdominal distension, drug eruption and rash. Severe TEAEs of elevated blood creatine phosphokinase noted in two subjects in the vonoprazan group were assessed as unrelated to study treatment. There were 5 subjects in the vonoprazan group who had ALT >3 × ULN assessed as related to all 4 components of quadruple therapy, which declined or resolved during follow up. There were no deaths or relevant clinical changes in laboratory tests/ ECG findings and no pregnancies reported during or after the study.

(b) (4), (b) (5)

Chemistry Manufacturing and Controls (CMC) PAS

The sponsor submitted a CMC PAS on June 30, 2023, to provide a new formulation for vonoprazan tablets, and to add (b) (4) release and shelf-life limits in the specification of the vonoprazan drug product. This supplement is under review by the CMC

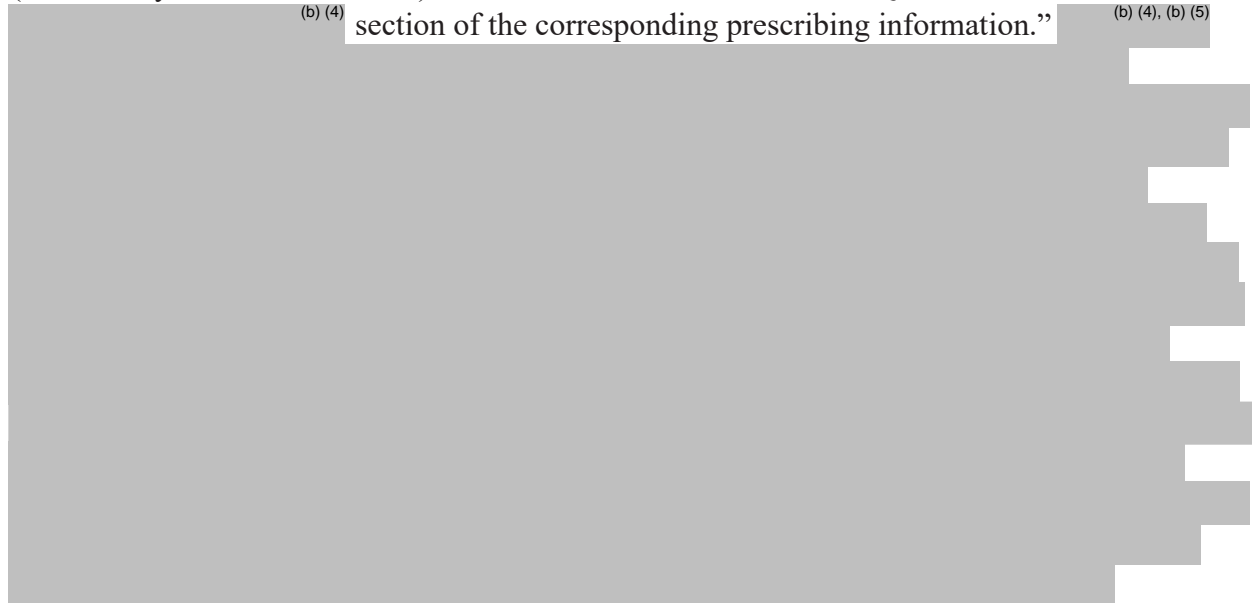
reviewer, awaiting the 6-month stability data for the blister packs. The supplement is also under review by the nonclinical reviewer to assess if the release limits are acceptable.

Conclusions

The safety profile of vonoprazan is similar to that of esomeprazole and it was well tolerated when used as a constituent of quadruple therapy for *H. pylori* eradication. (b) (4), (b) (5)



The draft PI for vonoprazan for healing of EE and maintenance of healing of EE submitted with NDA 215151 was reviewed with this consult. This reviewer notes hypersensitivity reactions, rash in patients with mononucleosis as well as several Warnings and Precautions due to the clarithromycin component, i.e., QT prolongation, hepatotoxicity, serious adverse reactions due to concomitant use with other drugs, embryo-fetal toxicity, and myasthenia gravis in the VOQUEZNA triple Pak and dual Pak approved PI. This MO recommends cross-referencing this information using the following language at the end of (b) (4) section of the NDA 215151 PI “For information about (b) (4) of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with VOQUEZNA, refer to the (b) (4) section of the corresponding prescribing information.” (b) (4), (b) (5)



Clinical reviewer

Mayurika Ghosh, MD

Mayurika Ghosh -S
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Date: 2023.08.30 12:13:53 -04'00'

Clinical team leader

Mark Needles, MD

Mark Needles -S
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Deputy Division Director, DAI

Dmitri Iarikov, MD, PhD

Dmitri E. Iarikov -S
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/s/

MAYURIKA GHOSH
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: Maureen Dewey, Regulatory Project Manager, Division of Gastroenterology (DG)

FROM: Jacqueline Yancy, Ph.D., Senior Regulatory Health Project Manager
Division of Pediatric and Maternal Health (DPMH)

DRUG: **Voquenza (vonoprazan)**

NDA: **215151**

DG submitted a consult request to DPMH dated May 30, 2023, to provide labeling review, PMR assistance and assistance with PeRC preparation for the Applicants (Phathom) NDA resubmission.

DPMH participated in the internal meetings with the Division and provided input on the development of PMRs as well as PeRC on October 3, 2023. DPMH does not have any additional comments or questions at this time.

This memorandum will close out the consult request.

DPMH RPM – Jacqueline Yancy
DPMH CPMS – George Greeley
DPMH Pediatric Medical Officer—Ramy Abdelrahman
DPMH Pediatric Team Leader— Mona Khurana
DPMH Maternal Health Medical Officer – Jane Liedtka
DPMH Maternal Health Team Leader – Tamara Johnson

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/s/

JACQUILINE A YANCY
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 8, 2023
Requesting Office or Division: Division of Gastroenterology (DG)
Application Type and Number: NDA 215151
Product Name and Strength: Voquezna (vonoprazan) tablets, 10 mg and 20 mg
Applicant/Sponsor Name: Phathom Pharmaceuticals, Inc.
OSE RCM #: 2022-708
DMEPA 1 Safety Evaluator: Sherly Abraham, R.Ph.
DMEPA 1 Team Leader: Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant resubmitted revised container labels and carton labeling received on May 19, 2023 for Voquezna. The Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for Voquezna (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

1. 1 Regulatory History

Phathom Pharmaceuticals, Inc previously submitted a new NDA (NDA 215151) for Voquezna on May 25, 2022. We completed a label and labeling review and two label and labeling memos and provided recommendations for Phathom; however, the application received a complete response (CR) on February 7, 2023 due to product quality issues.^{a, b, c} Phathom responded to the

^aAbraham, S. Label and Labeling Review for Voquezna (NDA 215151). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 31. RCM No.: 2022-555

^bAbraham, S. Label and Labeling Review Memo for Voquezna (NDA 215151). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 3. RCM No.: 2022-555-1

^cAbraham, S. Label and Labeling Review Memo for Voquezna (NDA 215151). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 9. RCM No.: 2022-555-2

CR for NDA 215151 and re-submitted the Voquezna label and labeling for our review on May 19, 2023.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Pharmacovigilance Memorandum

Date: August 8, 2023

Reviewer: Jamie Ridley Klucken, PharmD, MBA, BCPS, BCACP
Safety Evaluator, Division of Pharmacovigilance I (DPV-I)

Acting Team Leader: Scott Janiczak, PharmD, BCPS
DPV-I

Acting Deputy Director: Lisa Wolf, PharmD, BCCCP
DPV-I

Product Name: Voquenza (vonoprazan fumarate)

Subject: Erectile dysfunction

Application Type/Number: NDA 215151

Applicant: Phathom Pharmaceuticals Inc.

TTT Record ID: 2023-5518

1 INTRODUCTION

The purpose of this memorandum is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of Gastroenterology (DG) an evaluation of erectile dysfunction (ED) associated with vonoprazan from the FDA Adverse Event Reporting System (FAERS) database, the literature, and cases the Applicant identified in clinical trials and their global safety database. Information from this review will assist DG in their evaluation of the resubmission of NDA 215151 Voquezna (vonoprazan fumarate).

1.1 BACKGROUND

On March 11, 2022, the Applicant submitted NDA 215151 for single-ingredient vonoprazan, a novel potassium-competitive acid blocker (P-CAB), indicated for healing of erosive esophagitis and relief of heartburn, maintenance of erosive esophagitis and healing of heartburn and treatment of *Helicobacter pylori* infection. Multi-ingredient products containing vonoprazan were approved by FDA on May 3, 2022, for the treatment of *Helicobacter pylori* infection. During the NDA review for single ingredient vonoprazan, DG issued a Safety Labeling Change (SLC) for all prescription Proton Pump Inhibitor (PPI) products, adding the term “erectile dysfunction” to product labeling based on postmarketing cases identified. DG consulted DPV to determine if there were any postmarketing cases of ED with vonoprazan given the similar mechanism of action^a and adverse event profile to PPIs. A timeline of key events are noted below.

- December 26, 2014: Vonoprazan was approved in Japan for the treatment of acid-related diseases.¹
- September 24, 2021: FDA opened a newly identified safety signal (NISS) for the potential risk of ED associated with Proton Pump Inhibitors (PPIs) (SS ID 1004603) after identification of a new case report² published in the medical literature describing “...the abrupt onset of profound ED in a healthy young man after initiating over-the-counter omeprazole therapy, with erectile function rapidly normalizing following discontinuation of the drug.” The NISS was moved to the evaluation phase on December 21, 2021.
- January 14-19, 2022: FDA notified all Applicants of products containing PPIs of this NISS.
- March 11, 2022: Phathom Pharmaceuticals Inc. submitted NDA 215151 for single ingredient vonoprazan.
- May 3, 2022: NDA 215152 Voquezna Triple Pak (amoxicillin, clarithromycin, vonoprazan fumarate) and NDA 215153 Voquezna Dual Pak (amoxicillin, vonoprazan fumarate) were approved by FDA for treatment of *Helicobacter pylori* infection. These products are not currently distributed for domestic or foreign use.³

^a PPIs irreversibly inhibit hydrogen potassium-ATPases, which produce acid in gastric parietal cells. P-CABs reversibly inhibit hydrogen potassium ATPases.

- October 24, 2022: DPV-I completed a cumulative review⁴ of 1) all reports with the Preferred Term *Erectile Dysfunction* with all single-ingredient PPI products received to the FAERS database through July 4, 2022, 2) all published case reports of ED with PPI products in Embase and PubMed through July 29, 2022, and 3) Takeda’s global safety database. After applying strict case selection criteria and assessing for a causal relationship between the event and PPI therapy, DPV-I included 34 possible or probable postmarketing cases of ED across the PPI class in the case series. DPV-I recommended harmonization of prescription PPI labeling based on identification of postmarketing cases of ED with all PPI products and possible biologic mechanisms suggestive of a class effect. The results of the review were shared with the NISS team, including DG and the Division of Nonprescription Drugs I (DNPD-I); the NISS team concluded that class labeling via SLC for prescription PPI products was warranted.
- December 14, 2022: FDA submitted an Information Request (IR)⁵ to Phathom Pharmaceuticals Inc. to conduct a search of their clinical trials and global safety databases for cases of ED following exposure to vonoprazan.
- February 7, 2023: A complete response⁶ was issued for NDA 215151 (single ingredient vonoprazan) due to product quality issues.
- April 14, 2023: FDA sent an SLC notification to all Applicants of prescription PPI products with required labeling changes to ADVERSE REACTIONS *Postmarketing Experience*, adding the term “erectile dysfunction.” Notably, “impotence” is listed in Section 6.1 *Clinical Trials Experience* for oral prescription esomeprazole magnesium products and for oral and intravenous (IV) prescription lansoprazole products.
- May 19, 2023: The Applicant submitted a 505(b)(1) class 2 resubmission for NDA 215151. As part of the resubmission, the Applicant submitted a response⁷ to FDA’s IR.^b

2 METHODS AND MATERIALS

DPV-I reviewed information from FAERS, the medical literature, and the Applicant’s IR response.

2.1 FAERS

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	July 12, 2023
Time period of search	All reports through July 11, 2023
Search type	<i>RxLogix PV Reports Quick Query</i>

^b The Applicant denied receiving the original IR from December 14, 2022. The Applicant acknowledged receipt of the IR via preliminary comments for the Type A meeting on March 3, 2023.

Table 1. FAERS Search Strategy*	
Product terms	PAI: AMOXICILLIN\CLARITHROMYCIN\VONOPRAZAN FUMURATE, AMOXICILLIN\METRONIDAZOLE\VONOPRAZAN, ASPIRIN\VONOPRAZAN FUMARATE, VONOPRAZAN, VONOPRAZAN FUMARATE
MedDRA search terms (Version 26.0)	PT: <i>Erectile dysfunction</i>
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PAI=Product Active Ingredient, PT=Preferred Term	

2.2 MEDICAL LITERATURE

DPV-I searched the medical literature with the strategy described in **Table 2**.

Table 2. Literature Search Strategy	
Date of search	July 12, 2023
Database	Search 1: Embase Search 2: PubMed@FDA
Search terms	Search 1: ('vonoprazan'/exp OR vonoprazan) AND ('erectile dysfunction'/exp OR 'erectile dysfunction' OR 'impotence'/exp OR impotence OR 'sexual dysfunction'/exp OR 'sexual dysfunction') Search 2: vonoprazan AND (erectile dysfunction OR impotence OR sexual dysfunction)
Years included in search	All

2.3 APPLICANT'S IR RESPONSE

The Applicant searched their clinical trials and global safety database for cases of ED following exposure to vonoprazan, as of March 31, 2023.

2.4 CASE DEFINITION AND CAUSALITY

Reports were assessed for inclusion in the case series if they reported difficulty getting or keeping an erection. Cases were assessed for a causal relationship between the adverse events and PPIs using a modified version of the World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality assessment tool (see **Table 3**).

Table 3. Causality Classification and Criteria based on the WHO-UMC System⁸	
Causality Term	Assessment Criteria
Certain	• Event with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)

Table 3. Causality Classification and Criteria based on the WHO-UMC System⁸	
	• Rechallenge satisfactory, if necessary
Probable	• Event with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event with reasonable time relationship to drug intake • Response to withdrawal clinically reasonable • Could also be explained by diseases or conditions (e.g., <u>diabetes, cardiovascular disease</u>), psychological factors (e.g., <u>anxiety, depression</u>), lifestyle factors (e.g., <u>obesity, smoking</u>), or other drugs (e.g., <u>antihypertensives, antidepressants, antipsychotics, antiandrogens, antihistamines, opiates, recreational drugs</u>)
Unlikely	• Event with an improbable time relationship to drug intake (but not impossible) • Disease or other drugs provide plausible explanations (e.g., <u>history of ED, recent prostate radiation/surgery or other active concurrent confounding conditions</u>) • Negative dechallenge/rechallenge
Unassessable	• Report suggesting an adverse reaction • No temporal relationship established • Cannot be judged because information is insufficient (i.e., <u>no dechallenge information</u>) or contradictory • Data cannot be supplemented or verified

3 RESULTS

3.1 FAERS

The search of FAERS retrieved one case, which is summarized below.

FAERS Case #21685688, Other serious outcome, Japan, 2023

This spontaneous case from a physician describes a 32-year-old male with diabetes, dyslipidemia, and myocardial infarction who experienced ED 9 days after initiating vonoprazan and other medications^c. Eight days after initiating vonoprazan (and other medications^c), the patient experienced “giddiness/lightheadedness” and was diagnosed with hypotension with blood pressure “in the latter half of 70-80.” The following day, the patient consulted the physician about ED that “developed after admission.” The next day, sacubitril/valsartan was “switched to another drug” and the patient fully recovered from hypotension. The patient was discharged on an unknown date; the outcome of ED was not reported.

Reviewer comment: This case describes a patient with confounding underlying disease and concomitant medications who experienced ED concurrent with hospitalization for

^c The patient started a cetylsalicylic acid, sacubitril/valsartan, prasugrel, rosuvastatin, dapagliflozin, bisoprolol, nicorandil, and vonoprazan on the same day.

hypotension/dizziness. Vonoprazan was not discontinued, and the outcome of ED is unknown. This case is deemed unlikely related to vonoprazan.

3.2 MEDICAL LITERATURE

The search of the medical literature retrieved no articles.

3.3 APPLICANT'S IR RESPONSE

The search of the Applicant's clinical trials and global safety database retrieved four cases. One case^d was retrieved in the FAERS search (see **Section 3.1** for a summary of this case). The remaining three cases are summarized below.

2018TJP032095, Non-serious, Japan

This spontaneous case from a healthcare professional describes a 56-year-old male who experienced ED an unknown time after initiating vonoprazan for reflux esophagitis. Multiple concomitant medications were used (details not provided). Past medical history, treatment, and outcome were not reported.

Reviewer comment: This spontaneous case describes ED an unknown time after initiating vonoprazan. This case is deemed unassessable as it did not contain adequate information to assess causality, such as a specific temporal relationship, possible confounders (e.g., medical history, concomitant medications), and medication dechallenge.

2021TEU005240, Serious, China, 2021

This case from a phase IV non-interventional postmarketing safety surveillance study describes a 34-year-old male who experienced ED 20 days after initiating, and 2 days after discontinuing, vonoprazan for gastroesophageal reflux disease. Concurrent medical conditions included tobacco use, alcohol use, lung nodules, and arthralgia. See **Table 4** below for the time course of medications and events.

Table 4. Time Course of Vonoprazan Therapy and Events		
Day	Vonoprazan Therapy	Event
0	Vonoprazan 20 mg daily initiated	
5		Reflux laryngitis
7		Arthritis
18	Vonoprazan withdrawn	
20		Erectile dysfunction
33		Allergic dermatitis
39		<i>Allergic dermatitis resolved</i>
67		<i>Erectile dysfunction resolved</i>
72		<i>Oropharyngeal pain resolved</i>

^d Manufacturer Control Number 2023TJP001355 is a duplicate of FAERS Case #21685688.

Reviewer comment: This case from a study describes ED following discontinuation of vonoprazan therapy in a patient with confounding alcohol and tobacco use. This case is deemed unlikely related as the event occurred following discontinuation of therapy.

002-1101002, Non-serious, Japan, 2011

This case from a clinical trial describes a 49-year-old male who experienced “mild” ED 2 days after initiating vonoprazan 20 mg for erosive esophagitis. Medical history includes glaucoma, diabetes mellitus, and dyslipidemia. Concomitant medications include betaxolol hydrochloride. Vonoprazan dosage was not changed. No additional information was provided.

Reviewer comment: This case from a clinical trial describes ED 2 days after initiation of vonoprazan therapy in a patient with confounding diabetes and dyslipidemia. Vonoprazan therapy was continued. This case is deemed unassessable given the lack of medication dechallenge and clinical outcome.

4 REVIEWER COMMENTS

Our search of the FAERS database, medical literature, and Applicant’s IR response for all reports of ED associated with vonoprazan products retrieved four unique cases. After applying the case definition and causality criteria, no reports were included in the case series. We are mindful of the fact that the absence of reporting does not necessarily mean the absence of a signal and that FAERS data has limitations, including under-reporting. Many factors can influence the reporting of an event, including the length of time a product has been marketed and publicity surrounding an event. However, based on the lack of supportive cases, we do not recommend inclusion of ED in labeling for vonoprazan products at this time.

5 APPENDICES

5.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population

6 REFERENCES

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2. Perry TW. Abrupt-onset, profound erectile dysfunction in a healthy young man after initiating over-the-counter omeprazole: a case report. J Med Case Rep. 2021;15(1):360.
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Clinical Inspection Summary

Date	December 29, 2022
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Maureen Dewey, Senior Regulatory Project Manager Laura Finkelstein, MD, Clinical Reviewer Joette Meyer, PharmD, Clinical Team Leader Julie Tomaino, MD, Division Director Division of Gastroenterology (DG)
NDA #	215151
Applicant	Phathom Pharmaceuticals, Inc.
Drug	Voquezna (vonoprazan)
NME	No
Proposed Indication	For the healing of all grades of erosive esophagitis (EE) and relief of heartburn in adults for up to 8 weeks and maintenance of healing of all grades of EE and relief of heartburn
Consultation Request Date	May 5, 2022
Summary Goal Date	January 4, 2023
Action Goal Date	January 11, 2023
PDUFA Date	January 11, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical Investigators, Drs. Mitev, Lowe, and Kopp, as well as (b) (4), the Contract Research Organization (CRO) who was responsible for performing critical study-related activities, were inspected in support of NDA 215151, covering one clinical trial, EE-301.

During the clinical investigator inspections, the source records documenting the primary and key secondary efficacy endpoint data related to healing and maintenance of healing of erosive esophagitis (EE) (i.e., local endoscopy and central adjudicator's endoscopy reads at Screening/Baseline and Weeks 2, 8, and 24) were reviewed and verified against the applicant's data line listings for 90 of the 144 randomized subjects at the 3 sites inspected. There were no discrepancies noted when reviewing the source records for the *central adjudicator's endoscopy reads* against the applicant's data line listings. In addition, no discrepancies were noted during inspection of Drs. Mitev (Site 35006) and Lowe (Site 10004) when reviewing the source records for the *local endoscopy reads* against the applicant's data line listings.

However, the local endoscopy source records, documenting the endoscopies performed and the local endoscopy reads by the sub-investigator were not available for review during inspection for 99 of the 103 (96%) endoscopies performed in all 35 randomized subjects enrolled by Dr. Kopp (Site 10010) at some or all timepoints (i.e., at Baseline/Screening, Week 2, Week 8, and Week 24). In an October 26, 2022 response to an IR, the applicant submitted certified copies of all local endoscopy source records for the 35 subjects randomized at this site. An internal OSI review of the certified copies of these source records was performed and 14 discrepancies in 12 subjects were noted when comparing the sub-investigator's local endoscopy source records against the applicant's data line listings for the local endoscopy read.

The following concerns related to these discrepancies were noted at Dr. Kopp's site (#10010):

- There were two local endoscopy reads at this site, one read performed by a sub-investigator with formal specialized training in gastroenterology who was delegated by Dr. Kopp to perform the endoscopies, and one by Dr. Kopp, the clinical investigator and an internist, who independently read all endoscopies and submitted his reads to the sponsor database (i.e., Dr. Kopp's local reads were submitted to the NDA in the SDTM dataset).
- There were differences noted in the two local endoscopy reads (i.e., performed by Dr. Kopp and by the sub-investigator) that possibly resulted in deviations in the protocol-required central adjudication process. For example, based on the local endoscopy source records (i.e., generated by the sub-investigator) submitted to the NDA, it appears that for 13 of the 14 endoscopies performed in 11 subjects, there were not two matching Los Angeles (LA) grade ratings of EE which should have initiated the protocol-required central adjudication process of a second central adjudicator assessment. See Section II for details regarding the central adjudication process and the importance of the local endoscopy read in this adjudication process.
- During inspection, study worksheets documenting Dr. Kopp's read were reviewed and verified against the data line listings. While no discrepancies were noted, these study worksheets were noted to have been completed and signed by Dr. Kopp after the central adjudicator's read was communicated to the site. In addition, Dr. Kopp's local reads that were entered directly by the study coordinator into (b) (4) system were not verified during the inspection.

Further described in Section III.3 of the CIS are details regarding the 14 discrepancies, including the 13 cases in 11 subjects, where based on the source records submitted by the applicant to the NDA, there appears to not be two matching LA grade ratings of EE.

In addition, the source records documenting a key secondary efficacy endpoint of the incidence 24-hour heartburn-free days (i.e., daytime and nighttime heartburn entries in the subject's eDiary) were reviewed and verified against the sponsor's data line listings for 30 of the 144 randomized subjects at the 3 sites. In a May 4, 2022 response to an IR, the applicant reported that there was a programming error in the (b) (4) electronic patient-reported outcome (ePRO) application that allowed subjects to make duplicate electronic diary (eDiary) entries when documenting their morning or evening heartburn incidence. The eDiary audit trails in these subjects were also reviewed to identify and assess the duplicate eDiary data reported to FDA.

No issues or discrepancies were noted. See Section III.4 for additional information and impact of the (b) (4) programming error allowing for duplicate data entries on the eDiary heartburn data.

Notwithstanding the inspection observations and the impact on the endoscopy data at Site 10010 summarized in Section III.3 of this CIS, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

NDA 215151 was submitted in support of the use of vonoprazan in adults, 18 years of age and older for the healing of all grades of erosive esophagitis (EE) and relief of heartburn as well as maintenance of healing of all grades of EE and relief of heartburn. A pivotal study supporting the application was the following:

- 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.”

Protocol EE-301 was a Phase 3, multicenter, two-phase, double-blind, noninferiority study of vonoprazan versus lansoprazole for the healing of all grades of EE and relief of heartburn as well as the maintenance of healing of all grades of EE and relief of heartburn. The primary objectives were:

- To assess the efficacy in maintenance of healing of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE
- To assess the safety of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE

Subjects:

- Healing Phase: A total of 4167 subjects were screened and 1027 were randomized (514 to vonoprazan 20 mg and 513 lansoprazole 30 mg); and 1024 subjects were treated (514 to vonoprazan 20 mg and 510 lansoprazole 30 mg)
- Maintenance Phase: A total of 893 subjects were screened and 1027 were randomized (298 to vonoprazan 10 mg; 298 to vonoprazan 20 mg; and 297 to lansoprazole 15 mg); and 889 subjects were treated (296 to vonoprazan 10 mg; 296 to vonoprazan 20 mg; and 297 to lansoprazole 15 mg)

Sites: The study was conducted at 111 study sites, including 77 sites in the US and 34 sites in Europe

Study initiation and completion dates: Oct 28, 2019 (first subject signed informed consent);

July 29, 2021 (last subject, last visit for the primary efficacy endpoint); and August 24, 2021 (last subject, last visit/contact)

Database Lock Date: Sep 29, 2021

Study Unblinding: Sep 29, 2021

The study consisted of the following:

- Screening Period (Day -35 to Day -2)
- Healing Phase (Healing Day -1 to Healing Day 15 or 57)
- Maintenance Phase (Maintenance Day 1 to Maintenance Day 169)
- Follow-up Period (4 weeks after the last dose of study drug)

During the screening period, subjects were evaluated for eligibility and those who met all eligibility criteria were entered in the study. The screening endoscopy was performed after the subject had fulfilled all other admission criteria and within 7 days (no later than 10 days on rare occasion with sponsor approval) prior to randomization.

During the screening endoscopy procedure, the investigator/endoscopist took pictures of the lower third of the esophagus documenting the investigator's/endoscopist's visual assessment of the subject's EE Los Angeles (LA) grade. These pictures were sent to (b) (4), a service provider contracted by the sponsor's contract research organization (CRO), (b) (4), to assign the endoscopist pictures uploaded by the site to a blinded central adjudicator.

The central adjudicator's endoscopy assessments were used to determine

- Eligibility (i.e., endoscopically confirmed EE of LA Classification Grades A to D during the Screening Period [Visit 1])
- Whether the subject's EE was healed during the Healing Phase or recurred during the Maintenance Phase

Central Adjudication Process:

The same blinded central adjudicator should have been assigned to review all of an individual subject's endoscope pictures. The adjudicator had up to 2 business days to review the endoscopic pictures and provide their assessment.

- If the adjudicator's rating agreed with the investigator, the subject was enrolled based on the central adjudicator's rating.
- If the adjudicator and investigator assessments were misaligned, a second blinded adjudicator reviewed the endoscopic pictures within another 2 business days. The subject was enrolled based on any 2 matching LA grade ratings.
- If there were 3 different ratings across the 2 adjudicators and the investigator, the 2 central adjudicators discussed their assessments and reached alignment on the LA grade rating. If the adjudicators were unable to reach consensus, the primary adjudicator's assessment was used to determine the subject's eligibility.

All other study-related endoscopies (e.g., at Weeks 2, 8, and 24) were evaluated in a similar

manner as described above. Once the adjudication process was completed, the central adjudicator's results were communicated to the investigator through (b) (4) system. In addition, the assessments performed by both the investigator and central adjudicator were entered into (b) (4), the EDC system that maintained the electronic case report forms (eCRFs) data at the clinical trial site. The investigator should not have changed his/her initial grading if the final assessment was different from their initial assessment.

During the Healing Phase, subjects with EE whose eligibility was confirmed were randomly assigned at baseline/randomization (Visit 2; Day -1) using an interactive response technology (IRT) system in a 1:1 ratio to one of the following treatments, given once daily for 8 weeks:

- Vonoprazan 20 mg plus matching placebo for lansoprazole 30 mg
- Lansoprazole 30 mg plus matching placebo for vonoprazan

The date of the first dosing was defined as Day 1. Healing was defined as endoscopically confirmed healing.

- An endoscopy was performed at Week 2.
- If endoscopic healing of EE was confirmed at Week 2, then the subject entered the Maintenance Phase.
- If endoscopic healing was not confirmed, then the subject continued to receive randomized treatment until Week 8.
- If endoscopic healing was confirmed at Week 8, the subject entered the Maintenance Phase.
- If endoscopic healing of EE was not confirmed at Week 8, the subject was discontinued from the study without entering the Maintenance Phase
- If the subject's EE was found to have healed at an unscheduled endoscopy visit, the subject was randomized into the Maintenance Phase.

During the Maintenance Phase, upon verification of healing, subjects were re-randomized using an IRT system in a 1:1:1 ratio to receive one of the following treatments, given once daily for 24 weeks:

- Vonoprazan 10 mg plus matching placebo for lansoprazole 15 mg
- Vonoprazan 20 mg plus matching placebo for lansoprazole 15 mg
- Lansoprazole 15 mg plus matching placebo for vonoprazan

If the subject was confirmed as healed and re-randomized to the Maintenance Phase, this visit was considered the baseline visit for the Maintenance Phase.

During the follow-up period, a safety Follow-up Visit was planned at 4 weeks after the last dose of study drug to assess adverse events and the serum gastrin level. Subjects who did not have EE healing at Week 8, and therefore discontinued the study after the Healing Phase, underwent the safety Follow-up Period.

Electronic patient reported outcome data:

(b) (4) contracted with (b) (4) a service provider, to handle and manage the electronic patient-reported outcome data. Subjects downloaded an electronic diary (eDiary) application

on his/her own phone during the Screening Period. For subjects who did not have a phone or whose phone did not support the eDiary application, the sponsor provided a device with the eDiary application downloaded on it.

Throughout the Screening Period (at least 7 days), Healing Phase, Maintenance Phase, and Follow-up Phase, subjects documented the presence and maximum severity of daytime and nighttime heartburn symptoms for a total of twice daily in their diary. The subject also provided information when they did not experience heartburn on any given day. The subject should have completed the eDiary every morning upon waking (to record the previous night's heartburn severity rating) and every evening before bedtime (to record that day's heartburn severity rating). The last entry that the subject made to their eDiary should have been on the morning of the Safety Follow-up Visit, prior to their site visit. The severity of heartburn was graded by the subject according to the following definitions:

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

Primary and Key Secondary Efficacy Endpoints:

The *primary efficacy endpoints* were as follows:

- For the Healing Phase, the percentage of subjects who had complete healing of EE by Week 8 as assessed by endoscopy per the central adjudicator's assessment
- For the Maintenance Phase, the percentage of subjects who maintained complete healing of EE after 24 weeks as assessed by endoscopy per the central adjudicator's assessment

Key secondary efficacy endpoints of interests were:

- For the Healing Phase:
 - The percentage of subjects who had complete healing of EE at Week 2 as assessed by endoscopy
 - The percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D
 - The percentage of subjects who have complete healing of EE by Week 8 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D
 - The percentage of 24-hour heartburn-free days over the Healing Phase as assessed by the patient's daily diary
- For the Maintenance Phase:

- The percentage of subjects who maintain complete healing of EE after 24 weeks as assessed by endoscopy for subjects with baseline LA Classification Grades C or D
- The percentage of 24-hour heartburn-free days over the Maintenance Phase as assessed by the daily diary

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site-specific efficacy results, and inspection history.

III. RESULTS (by site):

1. Stefan Andrey Mitev, MD

Site #35006
Saharov 20A
Sofia, 1784
Bulgaria

PDUFA Inspection Dates: July 18 to 22, 2022

At this site, 104 subjects were screened; 39 were randomized in the Healing Phase; 38 of the 39 experienced healing at Week 2 or Week 8 and were subsequently re-randomized in the Maintenance Phase. Thirty-eight of the 39 subjects completed the Healing Phase and 36 of these 38 subjects completed the Maintenance Phase.

Subject (b) (6) (randomized to vonoprazan 20 mg) withdrew consent during the Healing Phase for unspecified reasons. During the Maintenance Phase, Subject (b) (6) (randomized to vonoprazan 10 mg) withdrew consent for unspecified reasons and Subject (b) (6) (randomized to lansoprazole 15 mg) withdrew consent before the Week 24 visit due to planned international travel.

A full audit of the study records for the 39 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Ethics Committee submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints of healing of EE by Week 8 and maintenance of healing of EE by Week 24 and 24-hour heartburn-free days over Healing and Maintenance phases; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures, Form FDA 1572).

There was no evidence of under-reporting of adverse events, including bone-related adverse events (which were AEs of special interest to the review division). The source records documenting the primary and key secondary efficacy endpoint data for healing and maintenance of healing of EE (i.e., local and central adjudicator's endoscopy assessments at

Screening and Weeks 2, 8, and 24) were reviewed and verified against the sponsor's data line listings for the 39 randomized subjects. No discrepancies or issues were noted.

The source records documenting a key secondary efficacy endpoint of the incidence 24-hour heartburn-free days (i.e., daytime and nighttime heartburn entries in the subject's eDiary) were reviewed and verified against the sponsor's data line listings for 9 of the 39 subjects. No discrepancies were noted.

In addition, in a May 4, 2022 response to an IR, the applicant reported that there was a programming error in the (b) (4) ePRO application that allowed subjects to make duplicate eDiary entries when documenting their morning or evening heartburn incidence. During inspection, the eDiary audit trails in 9 of the 39 randomized subjects were reviewed to identify and assess the duplicate eDiary data reported to FDA. While it was noted that audit trails were difficult to understand and in some cases were not human readable, duplicate entries for these 9 subjects were verifiable in the audit trails. See Section III.4 for additional information and impact of the (b) (4) programming error allowing for duplicate data entries on the eDiary heartburn data.

2. John Lowe, MD

Site# 10004

Ridgeline Drive Suite A

Ogden, UT 84405

PDUFA Inspection Dates: August 15 to 19, 2022

At this site, 198 subjects were screened; 70 were randomized in the Healing Phase; 64 of the 70 experienced healing at Week 2 or Week 8 and were subsequently re-randomized into the Maintenance Phase; Sixty-seven of the 70 completed the Healing Phase and 58 of these 64 subjects completed the Maintenance Phase of the study.

Per the applicant's BIMO data line listings, during the healing phase, Subjects (b) (6) and (b) (6) (both randomized to vonoprazan 20mg) terminated early due to treatment-emergent adverse events (i.e., worsening of depression and maculopapular rash, respectively) and Subject (b) (6) (randomized to lansoprazole 30 mg) was lost to follow-up for unspecified reasons. During the Maintenance Phase, Subjects (b) (6) (randomized to vonoprazan 20 mg) and (b) (6) (randomized to vonoprazan 10 mg) were terminated early due to treatment-emergent adverse events (i.e., acute interstitial nephritis and maculopapular rash, respectively). Subjects (b) (6) (randomized to vonoprazan 10 mg) and (b) (6) (randomized to vonoprazan 20 mg) terminated early because both subjects relocated out of state. Subject (b) (6) (randomized to vonoprazan 10 mg) withdrew consent and Subject (b) (6) (randomized to lansoprazole 15 mg) was lost to follow-up, both for unspecified reasons.

Discrepancies were noted in the number of subjects screened at the site. The applicant reported that 186 subjects were screened. The following additional 10 subjects were noted on the site's enrollment log to have signed informed consent between Feb 2020 and March 2020:

(b) (6)

Reviewer's comment: *In an October 26, 2022 response to an IR, the applicant noted the reasons for screen failure for these 10 subjects as COVID-19-related. The sponsor had paused the study due to COVID-19-related issues, and these subjects were not enrolled during this time. All of these subjects were rescreened at a later date and were subsequently given new screening numbers. No further enrollment discrepancies were noted when comparing the applicant's response against the source records collected at the site for these 10 subjects.*

Two additional subjects were noted on the subject enrollment log to have signed informed consent; Subject (b) (6) signed informed consent on (b) (6), and Subject (b) (6) signed informed consent on (b) (6). Based on the subject enrollment log, Subject (b) (6) appears to have attended the randomization Visit 1 on (b) (6) and was a Screen Failure (SF)/Early Termination (ET) on (b) (6). Subject (b) (6) appears to have completed both the healing and maintenance phases. These subjects are not listed in the applicant's data line listings as having been enrolled in the trial and no study data, including efficacy data, appear to have been submitted for these subjects.

Reviewer's comment: *In an October 26, 2022 response to an IR, the applicant noted the following:*

- *Subject (b) (6) screen failed for inclusion criteria #2 (i.e., in the opinion of the investigator the subject is not capable of understanding and complying with protocol requirements due to subject having a pretreatment event of viral gastroenteritis). This same subject subsequently returned and signed informed consent; was rescreened in (b) (6); was randomized in the Healing Phase (randomized to vonoprazan 20mg) in (b) (6) and is included in the BIMO data line listings and SDTM dataset as Subject (b) (6).*
- *Subject (b) (6) was initially enrolled at this site in (b) (6) but was subsequently transferred to Site 10055 in (b) (6). This subject's data is included in the BIMO data line listings and in the SDTM dataset as Subject (b) (6).*

A full audit of the study records for 16 of the 70 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Institutional Review Board submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints of healing of EE by Week 8 and maintenance of healing of EE by Week 24 and 24-hour heartburn-free days over the Healing and Maintenance Phases; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures, Form FDA 1572).

There was no evidence of under-reporting of adverse events, including bone-related adverse events (which were AEs of special interest to the review division). The source records documenting the primary and key secondary efficacy endpoint data for healing and maintenance of healing of EE (i.e., local and central adjudicator's endoscopy assessments at Screening and Weeks 2, 8, and 24) were reviewed and verified against the sponsor's data line

listings for these 16 of 70 randomized subjects. No discrepancies or issues were noted

The source records documenting a key secondary efficacy endpoint of the incidence 24-hour heartburn-free days (i.e., daytime and nighttime heartburn entries in the subject's eDiary) were reviewed and verified against the sponsor's data line listings for these 16 of 70 randomized subjects. No discrepancies were noted.

In addition, in a May 4, 2022 response to an IR, the applicant reported that there was a programming error in the (b) (4) ePRO application that allowed subjects to make duplicate eDiary entries when documenting their morning or evening heartburn incidence. During inspection, the eDiary audit trails in these 16 of 70 randomized subjects were reviewed to identify and assess the duplicate eDiary data reported to FDA. While it was noted that audit trails were difficult to understand and in some cases were not human readable, duplicate entries were verifiable in the audit trails for these 16 subjects. See Section III.4 for additional information and impact of the (b) (4) programming error allowing for duplicate data entries on the eDiary heartburn data.

3. James Kopp, MD

Site# 10010

Greenville Street

Anderson, SC 29621

PDUFA Inspection Dates: August 23 to 25, 2022

At this site, 85 subjects were screened, 35 were randomized in the Healing Phase, and 32 of the 35 experienced healing at Week 2 or Week 8 and were subsequently re-randomized in the Maintenance Phase. Thirty-three of the 35 completed the Healing Phase and 27 of the 32 subjects completed the Maintenance Phase. During the healing phase, Subjects (b) (6) (both randomized to vonoprazan 20mg) were lost to follow-up for unspecified reasons. During the maintenance phase, Subjects (b) (6) (both randomized to vonoprazan 20mg) were lost to follow-up; Subjects (b) (6) (randomized to vonoprazan 20mg) and (b) (6) (randomized to lansoprazole 15 mg) withdrew consent for unspecified reasons; and Subject (b) (6) (randomized to lansoprazole 15 mg) was withdrawn by the clinical investigator for not complying with the study visit schedule.

Discrepancies were noted in the number of subjects screened at the site. The applicant reported in the data line listings submitted to the NDA that 83 subjects were screened whereas 85 subjects were noted to have been screened on the site's source records (i.e., site's enrollment log). Two subjects (i.e., Subjects (b) (6)) were noted on the site's enrollment log to have signed informed consent on (b) (6) and were subsequently noted to be screen failures.

Reviewer's comment: *In an October 26, 2022 response to an IR, the applicant noted the reasons for screen failure for these 2 subjects as COVID-19-related. The sponsor had paused the study due to COVID-19 and these subjects were subsequently not enrolled. However,*

these subjects were rescreened at a later date and were subsequently assigned new rescreening numbers, [REDACTED] ^{(b) (6)}, respectively. No further enrollment discrepancies were noted when comparing the applicant's response against the source records collected at the site for these 2 subjects.

A full audit of the study records for the 35 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Institutional Review Board submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints of healing of EE by Week 8 and maintenance of healing of EE by Week 24 and 24-hour heartburn-free days over the Healing and Maintenance Phases; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures).

There was no evidence of under-reporting of adverse events, including bone-related adverse events (which were AEs of special interest to the review division). The source records documenting the primary and key secondary efficacy endpoint data for healing and maintenance of healing of EE (i.e., local and central adjudicator's endoscopy assessments at Screening and Weeks 2, 8, and 24) were reviewed and verified against the sponsor's data line listings for the 35 randomized subjects. There were no discrepancies noted when reviewing the *central adjudicator's central endoscopy reports* documenting the central endoscopy read against the applicant's data line listings. However, it was noted that source records documenting the local endoscopy procedures and local endoscopy reads performed by the sub-investigator (the local endoscopist) for 99 of the 103 (96%) endoscopies performed in the 35 randomized subjects were not available at some or all timepoints (i.e., at Baseline/ Screening, Week 2, Week 8, and Week 24) for all randomized subjects.

During the inspection, these missing source records were discussed with Dr. Kopp, and he explained that he independently assessed the endoscopy images himself and his reads (and not the reads of the sub-investigator) were submitted to the sponsor. Thus, review of study worksheets that documented Dr. Kopp's read was also performed during inspection. While no discrepancies were noted between the study worksheets documenting Dr. Kopp's and the data line listings, these study worksheets were noted to have been completed and signed by Dr. Kopp after the central adjudicator's read was communicated to the site in all cases.

After the inspection, further follow-up with the applicant regarding these missing source records documenting the local endoscopy procedures was warranted. In an October 26, 2022 response to an IR, the applicant submitted certified copies of local endoscopy source records that documented in detail the endoscopy procedures and local reads performed by the sub-investigator. An internal OSI review of the certified copies of these source records was performed by this OSI reviewer to verify the local endoscopy reads against the applicant's data line listings and against information provided in the October 26, 2022 response to the IR). There were 14 discrepancies in 12 subjects noted and it appears that for 13 of the 14 endoscopies performed in 11 subjects, there were not two matching Los Angeles (LA) grade ratings of EE which should have initiated the protocol-required central adjudication process of

a second central adjudicator assessment. These discrepancies are further identified in Table 1 below.

Table 1: Description of discrepancies between the local endoscopy source record submitted to the NDA and the applicant’s data line listings of the local reads

Subject # Randomization (Summary of Efficacy Results)	Visit/Date of Endoscopy	Local Endoscopy Source Record (generated by the sub-investigator) submitted to the NDA	Data Line Listing Investigator’s Confirmed EE (Grade)	Data Line Listing Adjudicator’s Confirmed EE (Grade)	Two matching LA Grade Ratings Based on Local Endoscopy Source Records (generated by the sub- investigator) submitted to the NDA
(b) (6) Healing Phase (HP): • Vonoprazan (V) 20 (Healed Week 8) Maintenance Phase (MP): • V10 (Not Recurred)	Baseline (b) (6)	EE LA Grade A	EE LA Grade B	EE LA Grade B	No
(b) (6) HP: • V20 (Healed at Week 2) MP: • V20 (Not Recurred)	Baseline (b) (6)	EE LA Grade B	EE LA Grade C	EE LA Grade C	No
(b) (6) HP: • Lansoprazole (L) 30 (Healed at Week 2) MP: • V20 (Not Recurred)	Baseline (b) (6)	EE LA Grade A	EE LA Grade C	EE LA Grade C	No
(b) (6) HP: • V20 (Healed at Week 2) MP: • V10 (Not Recurred)	Baseline (b) (6)	EE LA Grade B	EE LA Grade A	EE LA Grade B	Yes
(b) (6) HP: • V20 (Healed at Week 2) MP: • V20 (Not Recurred)	Baseline (b) (6)	No EE noted	EE LA Grade A	EE LA Grade A	No

Clinical Inspection Summary
NDA 215151, Voquezna (vonoprazan)

(b) (6) HP: • V20 (Healed at Week 2) MP: • V10 (Not Recurred)	Baseline (b) (6)	EE LA Grade A	EE LA Grade B	EE LA Grade B	No
(b) (6) HP: • V20 (Healed at Week 2) MP: • V20 (Not Recurred)	Baseline (b) (6)	EE LA Grade B	EE LA Grade C	EE LA Grade C	No
(b) (6) HP: • L30 (Healed at Week 2) MP: • V10 (Not Recurred)	Baseline (b) (6)	EE LA Grade B	EE LA Grade C	EE LA Grade C	No
(b) (6) HP: • L30 (No Healed at Week; Healed at Week 8) MP: • L15 (Recurred)	Week 2 (b) (6)	EE LA Grade A	EE LA Grade B	EE LA Grade C	No
(b) (6) HP: • L30 (Not Healed at Week 2; Healed at Week 8) MP: • V10 (Not Recurred)	Week 2 (b) (6)	Healed	EE LA Grade A	EE LA Grade A	No
(b) (6) HP: • L30 (Not Healed at Week 2; Healed at Week 8) MP: • L15 (Recurred)	Week 8 (b) (6)	EE LA Grade A	Healed	Healed	No
(b) (6) HP: • L30 (Not Healed at Week 2; Healed at Week 8) MP: • L15 (Recurred)	Week 24 (b) (6)	EE LA Grade B	EE LA Grade C	EE LA Grade C	No
(b) (6) HP: • V20 (Healed at Week 2) MP: • L15 (Recurred)	Week 24 (b) (6)	EE LA Grade B	EE LA Grade C	EE LA Grade C	No

(b) (6)	Week 24 (b) (6)	Healed	EE LA Grade A	EE LA Grade C	No
HP: • V20 (Healed at Week 2) MP: • L15 (Recurred)					

Reviewer's comments: *These discrepancies in the local endoscopy source records (i.e., generated by the sub-investigator) for the local reads and the applicant's data line listings of the local reads as described in Table 1 resulted in the following concerns:*

- *Two local endoscopy reads being performed at this site (i.e., by Dr. Kopp and by the sub-investigator) with differences noted in the two local reads that possibly resulted in deviations in the protocol-required central adjudication process in 13 of the 14 discrepancies (i.e., based on the source records submitted to the NDA, it appears that two matching LA grade ratings may not have been obtained).*
- *The local endoscopy assessment data entered in (b) (4) by the study coordinator and the paper study worksheets, both which documented Dr. Kopp's reads, were noted to have been entered or completed (in (b) (4) or on the study worksheets, respectively) after the central adjudicator's reads were communicated to the site. Furthermore, Dr. Kopp's local read data entered by the study coordinator in (b) (4) systems was not assessed and verified during the inspection.*

This reviewer recommends that the review division account for these discrepancies in their review of this application per the discussion during the November 1, 2022 meeting with the clinical review team and FDA statisticians re: preliminary inspection observations of Site 10010.

OSI Supervisors' Comments:

According to the FDA Establishment Inspection Report (EIR), the inspection of Dr. Kopp did not find objectionable conditions and the efficacy endpoint data were verified at this site.

*The 14 discrepancies described in **Table 1** are related to the differences between the local reads made by the CI, Dr. Kopp, and his sub-investigator. Discrepancies between the CI's reads and the central adjudicator's reads in the line listings occurred in 3 subjects (# (b) (6) at Baseline, # (b) (6) at Week 2, # (b) (6) at Week 24).*

According to the Applicant's response to the IR dated October 26, 2022, the local reads were to be submitted through the (b) (4) web portal and then stored in (b) (4) database, (b) (4). Once the local reads were housed in (b) (4), the endoscopy images were to be sent to a blinded central adjudicator for an independent standardized review. The central adjudication process was only initiated after CI has submitted both the endoscopy images and the local reads. The central adjudicator was blinded to the local reads. The endoscopy-based efficacy endpoints were based on the central adjudicator's reads.

Dr. Kopp independently assessed the LA grades based on the endoscopy images, and submitted his reads directly into (b) (4), via the (b) (4) web portal. The protocol did not require the local reads to be made by a person with formal specialized training in gastroenterology. Dr. Kopp did receive protocol training for this study.

Since Dr. Kopp's local reads were housed in (b) (4), and not available during the inspection, these reads were not verified. Dr. Kopp also documented his reads in the paper worksheets which were verified during the inspection. These worksheets had dates after the site has received the central reads. Depending on the importance of the local reads to the review of this application, the review division may consider requesting the Applicant to verify Dr. Kopp's reads housed in the (b) (4) against his reads contained in the line listings submitted to the FDA.

The source records documenting a key secondary efficacy endpoint of the incidence 24-hour heartburn-free days (i.e., daytime and nighttime heartburn entries in the subject's eDiary) were reviewed and verified against the sponsor's data line listings for 5 of the 35 randomized subjects. No discrepancies were noted.

In addition, in a May 4, 2022 response to an IR, the applicant reported that there was a programming error in the (b) (4) ePRO application that allowed subjects to make duplicate eDiary entries when documenting their morning or evening heartburn incidence. During inspection, the eDiary audit trails in 5 of the 35 randomized subjects were also reviewed to identify and assess the duplicate eDiary data reported to FDA. While it was noted that audit trails were difficult to understand and in some cases were not human readable, duplicate entries were verifiable in the audit trails for these 5 subjects. See Section III.4 for additional information and impact of the (b) (4) programming error allowing for duplicate data entries on the eDiary heartburn data.

4.

(b) (4)
PDUFA Inspection Dates: (b) (4)

Phathom Pharmaceuticals, Inc. contracted with (b) (4), Inc and transferred regulatory responsibilities to them to perform critical clinical trial activities. (b) (4) was responsible for providing services related to (1) general clinical trial management and oversight of study conduct; (2) clinical trial drug supplies and drug accountability; (3) use of (b) (4) central laboratories; (4) clinical trial monitoring; (5) pharmacovigilance, medical monitoring, and expedited safety reporting submissions; (6) data collection, handling, and management, including use of contracted service providers to handle and manage endoscopy and ePRO data; (7) biostatistics; and (8) medical writing (e.g., writing the clinical study report and patient narratives, and generating tables, listings and figures).

The inspection covered roles and responsibilities; the organization and its personnel; registration of studies on clinicaltrials.gov; oversight of the clinical trial conduct, monitoring

procedures and activities; (b) (4) quality management system; drug accountability; adverse event reporting; process for managing protocol deviations; data collection, handling, and management, including use of service providers who handled and managed critical study data (e.g., endoscopy and ePRO data); record retention; statistical analysis processes and procedures; and financial disclosure. Records reviewed during the inspection included investigator agreements; service provider agreements and contracts; written standard operating procedures; handling and processing of protocol deviations; validation and other documentation related to the operational use of electronic systems, including the electronic Systems used to manage endoscopy and ePRO data (e.g., (b) (4) system and (b) (4) ePRO application and online portal); adverse event reporting; drug accountability records; relevant communication and correspondence; and monitoring activities.

An issue related to design and validation of the ePRO devices was noted in a May 4, 2022 response to an IR. In the applicant's response, they reported that there was a programming error in the (b) (4) ePRO application that allowed subjects to make duplicate eDiary entries when documenting their morning or evening heartburn incidence. The applicant also provided a listing of daily diary entries with duplicated records and initially reported that the duplicate entries occurred in 42 of 177 subjects randomized and impacted 232 of over 30,000 diary entries (or 0.73%). However, in a June 8, 2022 follow-up response, they further clarified that at the completion of the study, that 569 of 1024 subjects or about 56% of subjects in the mITT analysis set had at least one duplicate entry which occurred in 2304 of the 369748 (0.62%) of the individual diary entries. Of the duplicate entries, there were 93 instances where the presence or absence of heartburn changed in 64 total subjects. In addition, there were 128 instances where the reported severity of heartburn changed in 85 total subjects. In these cases, the applicant used the worst-case scenario (i.e., the presence of heartburn with the highest severity grade entered by the subject). During inspection, validation summary reports, including user acceptance testing documentation were reviewed. While the inspector stated that no issues were found, from review of the inspection exhibits, there appears to be a lack of oversight by (b) (4) of the initial validation that was performed by the service provider, as well as a lack of follow-up by (b) (4) to ensure that the initial validation issues were resolved before the ePRO devices went live (i.e., in production). In addition, after the programming error was noted by (b) (4), no quality event report was opened by (b) (4) to remediate the duplicate diary issue.

Reviewer's comment: *In a June 8, 2022 response to a May 27, 2022 IR, the applicant further noted that in those instances where the reported severity of heartburn changed, the worst-case result was used in the analysis. In addition, only a small percentage of the total ePRO data was impacted by the programming error. The applicant's response addresses our concerns regarding the duplicate data entry by subjects regarding their incidence of daytime and nighttime heartburn.*

{ See appended electronic signature page }

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Phillip Kronstein, M.D.
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Jenn Sellers, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA 215151
DG/Project Manager/Maureen Dewey
DG/Medical Reviewer/Laura Finkelstein
DG/Medical Team Leader/Joette Meyer
DG/Division Director/Julie Tomaino
OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Acting Branch Chief/Jenn Sellers
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/GCP Program Analysts/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHERYL A GRANDINETTI
12/30/2022 12:58:44 PM

PHILLIP D KRONSTEIN
12/31/2022 10:29:03 AM

JENN W SELLERS
01/03/2023 08:54:20 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 22, 2022

To: Maureen Dewey, MPH, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology (DG)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Meeta Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): VOQUEZNA (vonoprazan)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 215151

Applicant: Phathom Pharmaceuticals, Inc.

1 INTRODUCTION

On March 11, 2022, Phathom Pharmaceuticals, Inc. submitted for the Agency's review an Original New Drug Application (NDA) and Comparability Protocol for VOQUEZNA (vonoprazan) tablets, for oral use (NDA 215151).

The proposed indication for VOQUEZNA (vonoprazan) tablets, for oral use is for the:

- Healing of all grades of erosive esophagitis and relief of heartburn.
- Maintenance of healing of all grades of erosive esophagitis and relief of heartburn.
- Treatment of *Helicobacter pylori* (*H. pylori*) infection.

On December 2, 2022, the Applicant submitted for the Agency's review, a Response to FDA Labeling including a draft Patient Package Insert (PPI) as requested by the Agency.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology (DG) on May 20, 2022, and May 23, 2022, respectively for DMPP and OPDP to review the Applicant's proposed PPI for VOQUEZNA (vonoprazan) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft VOQUEZNA (vonoprazan) tablets, for oral use PPI received on December 2, 2022, and received by DMPP and OPDP on December 14, 2022.
- Draft VOQUEZNA (vonoprazan) tablets, for oral use Prescribing Information (PI) received on March 11, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 14, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NYEDRA W BOOKER
12/22/2022 11:53:57 AM

MEETA N PATEL
12/22/2022 03:39:51 PM

LASHAWN M GRIFFITHS
12/22/2022 03:41:57 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 22, 2022

To: Maureen Dewey Project Manager, (DG)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for VOQUENZA (vonoprazan) tablets, for oral use

NDA: 215151

In response to DG's consult request dated May 23, 2022, OPDP has reviewed the proposed product labeling (PI) and patient information (PPI).

OPDP has one comment on the PI, received on December 14, 2022 by electronic mail.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI was sent under separate cover on December 22, 2022.

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
12/22/2022 04:25:14 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 9, 2022
Requesting Office or Division: Division of Gastroenterology (DG)
Application Type and Number: NDA 215151
Product Name and Strength: Voquezna (vonoprazan) tablets, 10 mg and 20 mg
Applicant/Sponsor Name: Phathom Pharmaceuticals, Inc.
OSE RCM #: 2022-555-1
DMEPA 1 Safety Evaluator: Sherly Abraham, R.Ph.
DMEPA 1 Team Leader: Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 2, 2022 for Voquezna. The Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for Voquezna (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^aAbraham, S. Label and Labeling Review for Voquezna (NDA 215151). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 3. RCM No.: 2022-555-1

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/s/

SHERLY ABRAHAM
12/09/2022 09:25:44 AM

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12/09/2022 09:31:03 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: November 21, 2022

Reviewer(s): Lisa Wolf, PharmD, BCCCP, Team Leader
Division of Pharmacovigilance I (DPV-I)

(Deputy) Division Director(s): CDR Monica Muñoz, PharmD, PhD, BCPS
DPV-I

Product Name(s): Voquezna (vonoprazan)

Subject: Review of postmarketing safety

Application Type/Number: NDA 215151

Applicant: Phathom Pharmaceuticals Inc

TTT #: 2022-1781

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EXECUTIVE SUMMARY

This pharmacovigilance review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology (DG), contains an analysis of the FDA Adverse Event Reporting System (FAERS) database and the medical literature for an association between vonoprazan and adverse events specified by DG or identified by DPV-I as part of a high-level overview of the data sources. In addition, a response to an Information Request issued to the Applicant on September 29, 2022, is incorporated into the analysis. This review will inform DG as they review a New Drug Application (NDA) for Voquezna (vonoprazan), submitted by the Applicant to FDA, on March 11, 2022.

Vonoprazan is an acid-inhibitory agent called a potassium-competitive acid blocker (PCAB) and works similarly to proton pump inhibitors (PPIs), inhibiting hydrogen potassium (H⁺, K⁺) ATPase at the final step in the acid secretory pathway in gastric parietal cells. Vonoprazan is currently available in 16 foreign countries, first being approved in Japan in 2014. Additionally, Voquezna Triple Pak (215152) and Dual Pak (NDA 215153), which contain vonoprazan co-packaged with amoxicillin and clarithromycin or amoxicillin, respectively, were recently FDA-approved on May 3, 2022, for the treatment of *H. pylori* in adults.

With respect to the adverse events specified by DG, DPV-I did not identify any new safety information to support changes to the proposed Voquezna product labeling for the events of hepatotoxicity, bone fracture, lupus, *Clostridium difficile* infection, fundic gland polyps, and hypersensitivity. However, DPV-I identified postmarketing cases of thrombocytopenia, vitamin B₁₂ deficiency, and hypomagnesemia (including other electrolyte abnormalities) that were deemed plausibly associated with vonoprazan use and recommended changes to the proposed Voquezna product labeling. These events and accompanying labeling recommendations are discussed below.

DPV-I identified the events of gastric adenocarcinoma, select endoscopic/histopathologic findings (e.g., gastric erythema, parietal cell protrusions, oxyntic gland dilatation), and gastrointestinal candidiasis from the high-level overview of FAERS and the medical literature. However, DPV-I did not find sufficient evidence of a plausible causal association between the events (i.e., gastric adenocarcinoma, gastrointestinal candidiasis) and vonoprazan use or determined the events (i.e., endoscopic/histopathologic findings) to be consistent with the underlying mechanism of the drug and reasonably captured in the proposed Voquezna product labeling.

Thrombocytopenia

DPV-I identified one Japanese publication containing two cases of suspected drug-induced immune thrombocytopenia from the medical literature with possible causal association with vonoprazan use; both cases noted positive dechallenge to vonoprazan, although one case was also treated with a short course of steroids. DPV-I suggests addition of the term, thrombocytopenia, to the ADVERSE REACTIONS *Postmarketing Experience* section of Voquezna product labeling based on these few cases.

Vitamin B₁₂ Deficiency

DPV-I identified one well-documented case of vitamin B₁₂ deficiency possibly associated with vonoprazan use. Although the patient was elderly with atrophic gastritis, which represent risk factors for the event, vonoprazan could have contributed to the event particularly in a vulnerable patient. Inhibition of gastric acid secretion could theoretically promote malabsorption of cobalamin by multiple mechanisms and for consistency with PPI product labeling, DPV-I recommends elevating vitamin B₁₂ deficiency to the WARNINGS AND PRECAUTIONS section of the Voquezna product labeling. This labeling would also be consistent with PPI product labeling.

Hypomagnesemia

DPV-I identified three cases in which patients experienced hypomagnesemia and other related electrolyte abnormalities (hypokalemia n=3, hypocalcemia n=2) possibly associated with vonoprazan use. Although it is difficult to assess the response to dechallenge in these cases, DPV-I noted that all three cases described resolution of the electrolyte abnormalities after electrolyte replacement and vonoprazan discontinuation; two cases explicitly mentioned that there was no further recurrence. Two cases were noteworthy as the patients presented with critically low magnesium levels (0.2-0.4 mg/dL) with clinically significant sequelae (seizures n=1, disturbances in gait/consciousness n=1). The remaining case was limited because the patient's actual electrolyte values were not reported, but the patient did experience neuromuscular manifestations with the reported electrolyte abnormalities. Based on the seriousness of the cases, DPV-I recommended that hypomagnesemia be elevated to the WARNINGS AND PRECAUTIONS section of the Voquezna product labeling. In addition, DPV-I recommended to add other electrolyte abnormalities, such as hypokalemia and hypocalcemia, to the new WARNINGS AND PRECAUTIONS subsection and ADVERSE REACTIONS *Postmarketing Experience*. This labeling would also be consistent with PPI product labeling.

1 INTRODUCTION

This pharmacovigilance review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology (DG), contains an analysis of the FDA Adverse Event Reporting System (FAERS) database and the medical literature for an association between vonoprazan and select adverse events (e.g., hepatic injury, severe cutaneous adverse reactions (SCAR)). In addition, a response to an Information Request (IR) issued to the Applicant, Phathom Pharmaceuticals, on September 29, 2022, is incorporated into the analysis. This review will inform DG as they review a New Drug Application (NDA) for Voquezna (vonoprazan), submitted by the Applicant to FDA, on March 11, 2022.

1.1 BACKGROUND AND REGULATORY HISTORY

Vonoprazan is an acid-inhibitory agent called a potassium-competitive acid blocker (PCAB).¹ Vonoprazan works similarly to proton pump inhibitors (PPIs), inhibiting hydrogen potassium (H⁺, K⁺) ATPase at the final step in the acid secretory pathway in gastric parietal cells. However, unlike PPIs, vonoprazan does not require the presence of acid for its activation.

On March 11, 2022, the Applicant submitted NDA 215151 for vonoprazan 10 mg and 20 mg tablets for the following indications:

- Healing of erosive esophagitis (EE) and relief of heartburn
- Maintenance of EE and healing of heartburn
- Treatment of *Helicobacter pylori* (*H. pylori*) infection (in combination with amoxicillin and clarithromycin)

Importantly, Voquezna Triple Pak (215152) and Dual Pak (NDA 215153), which contain vonoprazan 20 mg tablets co-packaged with amoxicillin and clarithromycin or amoxicillin, respectively, were recently FDA-approved on May 3, 2022, for the treatment of *H. pylori* in adults.² Vonoprazan is currently available in 16 foreign countries, first being approved in Japan in 2014.³

On September 22, 2022, DG consulted DPV-I to search FAERS for postmarketing reports of the following adverse events of special interest (AESIs) identified by the Applicant as related to acid suppression (and reported with PPIs) or unique to vonoprazan: hepatic dysfunction, cytopenias, bone fracture, lupus, *Clostridium difficile* (*C. difficile*), vitamin B₁₂ deficiency, hypomagnesemia, fundic gland polyps, anaphylaxis and anaphylactic shock, and hypersensitivity including drug eruption and erythema multiforme. In addition, DG requested DPV-I to 1) advise on reactions included in ADVERSE REACTIONS *Postmarketing Experience* of the proposed vonoprazan labeling, 2) to propose any additional terms for inclusion based on FAERS and literature data, and 3) to specifically comment on inclusion of thrombocytopenia (based primarily on a literature reference⁴) and hypomagnesemia in the labeling.

On September 29, 2022, FDA issued an IR to the Applicant to obtain additional postmarketing information for vonoprazan. On October 14, 2022, FDA received the Applicant's response to the IR.

1.2 RELEVANT PRODUCT LABELING

The proposed product labeling for Voquezna, submitted to FDA on May 25, 2022, contains the following safety information pertinent to this current review.^{a,b,2}

(b) (4)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in **Table 1**. For each individual adverse event discussed in **Section 3** of this review, we performed a subquery of the query in **Table 1** using Medical Dictionary for Regulatory Activities (MedDRA) terms specific to the event; the subquery terms are included in **Section 3**.

Table 1. FAERS Search Strategy*	
Date of search	September 27, 2022
Time period of search	All reports through September 26, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: vonoprazan, vonoprazan fumarate
* See Appendix A for a description of the FAERS database.	

2.2 LITERATURE SEARCH STRATEGY

DPV-I searched the medical literature with the strategy described in **Table 2** to identify case reports of any adverse event with vonoprazan.

Table 2. Literature Search Strategy		
Date of search	September 28, 2022	
Database	PubMed@FDA	Embase
Search terms	Vonoprazan; filtered to case reports only	'vonoprazan'/exp OR vonoprazan AND 'case report'/de
Years included in search	All	All

2.3 CAUSALITY CRITERIA

Reports were assessed for a causal relationship between the adverse events and vonoprazan, using a modified version of the World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality assessment tool (see **Table 3**). Reports assessed as “unassessable” or “unlikely” were excluded from further review.

Table 3. Causality Classification and Criteria based on the WHO-UMC System⁵	
Causality Term	Assessment Criteria
Certain	• Event with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable	• Event with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event with reasonable time relationship to drug intake • Response to withdrawal clinically reasonable • Could also be explained by diseases or conditions
Unlikely	• Event with an improbable time relationship to drug intake (but not impossible) • Disease or other drugs provide plausible explanations • Negative dechallenge/rechallenge
Unassessable	• Report suggesting an adverse reaction • No temporal relationship established • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

2.4 IDENTIFICATION OF NEW POTENTIAL SAFETY SIGNALS

DPV-I performed two analyses to identify any additional adverse events of interest requiring further review from our search in **Table 1**. We performed a high-level analysis of the top 50 MedDRA Preferred Terms (PTs) with vonoprazan and a high-level analysis of reports containing Designated Medical Events (DMEs). See **Appendix B** for the details of our high-level analyses.

Of note, DMEs are adverse events that are considered serious and, from a pharmacovigilance perspective, may often be caused by exposure to drugs from many pharmacological or therapeutic classes. Identification of these events is a priority, even when the number of cases is small, and before there is evidence of disproportional reporting. DMEs are not intended to include events with a high prevalence in the general population. See **Appendix C** for a list of the Office of Surveillance and Epidemiology’s (OSE) DMEs.

3 RESULTS

The search strategy in **Table 1** retrieved 370 reports^c. The literature searches in **Table 2** retrieved 11 relevant case reports.^{4,6,7,8,9,10,11,12,13,14,15} Reports pertinent to the AESIs specified in the consult request^d are summarized below (**Section 3.1-3.9**) as well as potential safety signals identified from a high-level analysis of FAERS (see **Section 2.4** for details) and medical literature (**Section 3.10-3.13**). Of note, laboratory value units are documented in the following signal assessments if provided by the reporter.

3.1 HEPATOTOXICITY

Liver function test abnormal (*Clinical Trials Experience*) and hepatic injury, hepatic failure, and jaundice (*Postmarketing Experience*)^e are listed in the ADVERSE REACTIONS section of the proposed Voquezna product labeling. Hepatotoxicity (*Postmarketing Experience*) and abnormal liver function tests (*Laboratory Values*) are also included in the ADVERSE REACTIONS section of PPI product labeling^f.

Our search of the FAERS database identified 44 reports and search of the medical literature identified zero case reports. Of the 44 reports, 43 were deemed not plausibly related to vonoprazan use for one or more of the following reasons: duplicates, contained alternative causes (e.g., underlying disease, concomitant medications), contained limited information for assessment (i.e., unassessable), or did not describe hepatotoxicity (e.g., a report was retrieved of hypoalbuminemia). The remaining case (FAERS case # 20721227) describes the occurrence of increased liver function tests (LFTs) possibly due to a drug-drug interaction (DDI) between bosentan and vonoprazan; however, based on the information in the case, vonoprazan by itself may also be considered as a possible cause of the events. This case is summarized below.

FAERS Case # 20721227, Other Important Medical Event, JPN, 2022: A literature publication describes a 56-year-old male taking lansoprazole for reflux esophagitis and bosentan for limited cutaneous systemic sclerosis (SSc). Seven months after starting bosentan, his skin lesions were stable, but his esophagitis worsened, so he was switched to vonoprazan. Six months later, his aspartate aminotransferase (AST) was elevated to 490 U/L (normal range 13-33) and alanine aminotransferase (ALT) was elevated to 524 U/L (normal range 8-42); alkaline phosphatase and total bilirubin (Tbili) were within normal limits (WNL). Viral serologies for active hepatitis A, B, and C, cytomegalovirus, and Epstein-Barr virus were negative. One month after discontinuation of bosentan and vonoprazan, his liver dysfunction returned to normal but his skin on his fingers hardened. He was restarted on bosentan and lansoprazole. “Liver function normalized completely within 1 month of resuming bosentan and lansoprazole combination therapy.” There were no signs of further liver abnormalities or new digital ulcers after another 3 months. The authors suggest the liver function abnormalities occurred as a result of a DDI

^c The 370 reports originated from the following countries: Japan (365), Brazil (4), China (1).

^d hepatic dysfunction, cytopenias, bone fracture, lupus, *Clostridium difficile*, vitamin B12 deficiency, hypomagnesemia, fundic gland polyps, anaphylaxis and anaphylactic shock, and hypersensitivity including drug eruption and erythema multiforme

^e These terms are also contained in the *Postmarketing Experience* section of the approved Voquezna Triple Pak and Dual Pak product labeling in the vonoprazan section.

^f Prevacid (lansoprazole) product labeling was used as the reference product since lansoprazole was the comparator in the vonoprazan clinical studies. If the adverse event appeared in the Prevacid product labeling, we considered it a labeled adverse event for the PPI class.

between bosentan and vonoprazan mediated by an inhibitory effect of vonoprazan of cytochrome P450 (CYP) 3A4.

Reviewer comment: Bosentan is an endothelin receptor antagonist mainly metabolized by CYP2C9 and CYP3A.¹⁶ Coadministration of bosentan with both a CYP2C9 inhibitor and strong or moderate CYP3A inhibitor will likely lead to large increases in plasma concentrations of bosentan, and is therefore not recommended. The bosentan U.S. product labeling contains a boxed warning for hepatotoxicity.

Vonoprazan is noted to be a weak CYP3A inhibitor in the proposed Voquezna product labeling. The authors of the publication theorize that the addition of vonoprazan, a weak CYP3A4 inhibitor, resulted in a DDI with bosentan, which in turned caused the liver transaminase elevations. Alternatively, it is possible that the introduction of vonoprazan caused the LFT elevations, that subsided after drug discontinuation.

The Applicant identified 167 cases involving 179 events reported from post-marketing sources for the PTs hepatitis, hepatitis acute, drug-induced liver injury, hepatic failure, liver disorder, and jaundice. Ninety-three events from 83 cases were serious and 86 events were nonserious. They found the majority of the cases to be confounded by the use of other concomitant medications or concurrent medical conditions or the cases lacked sufficiently detailed information to rule-out other plausible causes of the reported event. They “did not definitively identify any index case of hepatitis, hepatitis acute, drug-induced liver injury, hepatic failure, liver disorder, or jaundice as being causally associated with the use of vonoprazan.” (b) (4)

We reviewed the CIOMS reports provided in Appendix D of the Applicant’s IR response. In general, we agree with the Applicant that many cases were confounded by concomitant medications or co-morbidities or contained limited information for assessment. Notably, on page 455 of Appendix D of the IR response, we identified one possible case of clinically significant drug-induced liver injury resulting in hepatic failure. This case from Japan describes a 71-year-old male who drank 2 coffee-cups of Japanese sake per day who was admitted to the hospital for urgent endoscopic hemostasis with clipping of a gastric ulcer. On day 2, he received 2 units of packed red blood cells (PRBCs). On day 4, he was started on vonoprazan 20 mg daily for treatment of the gastric ulcer hemorrhage. On day 6, he was transfused again with 2 units of PRBCs. On day 7, he was started on polaprezinc 150 mg/day for zinc deficiency. On day 10, AST and ALT were 24 and 21, respectively. On day 11, he was transfused with 4 units PRBCs.

At his first outpatient visit after discharge, 22 days after starting vonoprazan, severe hepatitis was noted with an AST of 3,703, ALT of 1,160, and Tbili of 3.2. The patient was referred to the hospital, and vonoprazan and polaprezinc were discontinued. The next day, his laboratory values were: AST 2,185, ALT 1,068, Tbili 3.03, direct bilirubin 0.75, INR 5.96, and platelet count 84,000. He was treated with fluids and supportive therapy including glycyrrhizin/glycine/cysteine. On day 9, his laboratory values were: AST 61, ALT 207, INR 1.23, and Tbili 20.77. On day 12, hematemesis and bloody bowel discharge were noted with a drop in hemoglobin from 11 to 7, and he was hypotensive (systolic blood pressure between 70-

80). Endoscopy revealed necrotizing esophagitis and hemostasis was achieved with PPI infusion and transfusion. He also had disturbed consciousness with ammonia levels between 200 to 300, which did not improve despite treatment with lactulose enema. On day 14, he was transferred to the intensive care unit and underwent plasma exchange and continuous hemodiafiltration therapies (continued through the next day). On day 16, his consciousness returned to normal and he was moved to the general ward 5 days later. On day 42, his laboratory values were: AST 50, ALT 19, Tbili 2.64, and INR 1.75. On an unknown date, a physician from the other hospital reported that the “LLT test” for vonoprazan and polaprezinc were positive and various unspecified virus tests were negative. A few months later, hepatic insufficiency was noted as resolved.

Reviewer comment: This case describes Drug-Induced Liver Injury Network (DILIN)¹⁷ grade 4^g severity liver failure possibly related to vonoprazan. It is notable that the patient was also started on polaprezinc at the same time as vonoprazan; polaprezinc is a chelated form of zinc and L-carnosine approved in Japan for the treatment of gastric ulcers. Additionally, the patient had a history of alcohol use. This single case is not sufficient to elevate liver failure to the WARNINGS AND PRECAUTIONS section of the Voquezna product labeling at this time, but does suggest that close pharmacovigilance monitoring is needed. We agree with inclusion of the hepatic-related adverse event terms in the ADVERSE REACTIONS Postmarketing Experience section at this time.

3.2 CYTOPENIAS

Various hematologic abnormalities are contained in PPI product labeling (e.g., leukopenia and thrombocytopenia in *Clinical Trials Experience*, pancytopenia and agranulocytosis in *Postmarketing Experience*). However, hematologic abnormalities are not included in the proposed Voquezna product labeling.

We retrieved 34 reports in the FAERS database.^h However, our hands-on review of the FAERS reports did not identify any cases of cytopenia plausibly associated with vonoprazan use. We deemed all the reports to be either unlikely related because of the presence of alternative causes (e.g., clopidogrel and agranulocytosis, zonisamide and leukopenia, chemotherapy, liver disease) and/or unassessable. Our literature search identified one Japanese publication^{4,i} describing two patients with suspected immune-associated thrombocytopenia induced by vonoprazan. The two cases are summarized^j below.

Case 1: A 72-year-old male with a baseline platelet count of 299,000/microL received vonoprazan for 14 days. He developed thrombocytopenia with a nadir platelet count of 4,000 /microL. His immature platelet fraction (IPF) was 20.9% and bone marrow aspiration showed

^g Met grade 4 severity because patient had elevation in serum ALT AND Tbili ≥ 2.5 mg/dL AND evidence of hepatic failure (INR ≥ 1.5 and encephalopathy).

^h MedDRA narrow SMQs used in search: Haematopoietic cytopenias, Haematopoietic cytopenias affecting more than one type of blood cell, Haematopoietic erythropenia, Haematopoietic thrombocytopenia, Haematopoietic leukopenia.

ⁱ This publication was also included in the consult by DG and included another case, which was deemed to be primary immune thrombocytopenia and not drug-induced.

^j Cases developed from Table 1 and text of the publication.

primary immune thrombocytopenia (ITP)-like features. Vonoprazan was discontinued, and he was treated with dexamethasone for 4 days; his platelet count improved immediately.

Reviewer comment: We agree with the authors of the literature publication that this is a possible case of drug-induced immune thrombocytopenia (DITP) associated with vonoprazan use. The short time-to-onset between vonoprazan initiation and development of thrombocytopenia, the severity of the thrombocytopenia (i.e., nadir platelet count <20,000/microL), and immediate improvement with drug discontinuation (and a short course of steroids) supports the causal association. The high IPF is more indicative of a hyperdestructive/consumptive process contributing to the thrombocytopenia and the biopsy findings are informative as DITP and ITP are typically clinically indistinguishable. Limitations of this case include that the reason for vonoprazan use was not provided. It would be helpful to know if vonoprazan was being used for H. pylori eradication, as this infection has been shown to contribute to the development of ITP¹⁸, and vonoprazan is used in combination with antibiotics that may also cause thrombocytopenia. In the publication, the authors discuss other patients who experienced thrombocytopenia in which vonoprazan was ruled out as a cause, therefore, we assume that other causes of thrombocytopenia (e.g., concomitant medications) were ruled out for this patient as well, but the full workup and details were not provided.

Case 2: A 54-year-old female with an initial platelet count of 153,000 /microL received vonoprazan for 106 days. She developed thrombocytopenia with a nadir platelet count of 28,000/microL. Vonoprazan was discontinued and her platelet count improved immediately. A bone marrow biopsy was not performed.

Reviewer comment: We agree with the authors of the literature publication that this is a possible case of drug-induced immune thrombocytopenia (DITP) associated with vonoprazan use. The time-to-onset of 106 days is longer than would be typically associated with a drug-induced cause. However, we do not have many case details to better understand if the true onset could have preceded the 106 days (e.g., did they draw labs based on symptoms or was it an incidental finding on routine screening). The case lacked robust clinical documentation, but the immediate improvement in platelet count after vonoprazan discontinuation and likely exclusion of other causes supports a possible association to vonoprazan use.

These two cases support the addition of thrombocytopenia to the ADVERSE REACTIONS Postmarketing Experience section of the Voquezna product labeling.

3.3 BONE FRACTURE

The potential risk of fracture is labeled in the WARNINGS AND PRECAUTIONS section of both approved PPI product labeling and the proposed Voquezna product labeling. The Voquezna Applicant's position is that, "Based on data from the clinical program and postmarketing reports, the risk of bone fracture with vonoprazan treatment appears to be very low. Nonetheless, since this is an identified risk associated with other acid-suppressing agents, bone fracture is included in the warnings and precautions section of the label."³

We retrieved eight FAERS reports^k and zero published literature cases of bone fracture in patients receiving vonoprazan. However, our hands-on review of the eight FAERS reports revealed zero cases of fracture plausibly associated with vonoprazan use. All eight reports described older patients ranging from 62 to 94 years of age; many patients had risk factors for the fracture event (e.g., osteoporosis, long-term steroid use, trauma, underlying medical history) and/or were receiving multiple medications with complex medical histories (e.g., rheumatoid arthritis, hepatitis C and hepatocellular carcinoma, diabetes mellitus) and lacked detailed accounts of the fracture event. The fracture events described in the reports included spine fracture (5), fracture not otherwise specified (2), and radius fracture (1).

Of note, one of the eight reports (FAERS Case # 9618108) with the PT Spinal compression fracture originated from a phase 3, double-blind, comparison of vonoprazan 10 or 20 mg for the prevention of recurrent gastric or duodenal ulcers during long-term therapy with nonsteroidal anti-inflammatory drugs. This report describes a 73-year-old female with pre-existing osteoporosis and rheumatoid arthritis treated with prednisolone, who was given vonoprazan for approximately 4 months; she experienced low back pain while gardening and went to the hospital and was diagnosed with an L4 compression fracture.

Reviewer comment: We did not find postmarketing cases of fracture plausibly associated with vonoprazan use, therefore, we defer to DG regarding the strength of clinical trial evidence and plausible mechanism to label fracture within the WARNINGS AND PRECAUTIONS section similar to PPIs.

3.4 LUPUS

Cutaneous and systemic lupus erythematosus is listed in the WARNINGS AND PRECAUTIONS section of PPI product labeling, however, is not included in the proposed Voquezna product labeling.

We retrieved zero FAERS reports^l and zero published literature cases describing any type of lupus in association with vonoprazan use.

Reviewer comment: We did not identify any postmarketing cases of lupus in association with vonoprazan use to support labeling. Although this reaction is noted in the WARNINGS AND PRECAUTIONS section for PPIs, we do not have sufficient evidence based on a plausible mechanism or case report evidence to recommend the same with Voquezna.

3.5 CLOSTRIDIUM DIFFICILE

Clostridium difficile (*C. difficile*)-associated diarrhea is listed in the WARNINGS AND PRECAUTIONS section of both PPI product labeling and the proposed Voquezna product labeling.

^k Search using High-Level Group Term *Fractures* retrieved the following eight FAERS case numbers: 14152179, 15679699, 15967263, 16647522, 17568603, 18461507, 20870083, 9618108.

^l Search used any PT containing “lupus” for FAERS report identification.

We retrieved six reports of *C. difficile* infection reported with vonoprazan use in the FAERS database.^m All six reports were confounded by use of or likely useⁿ of concomitant antibiotics (n=5) or use of chemotherapy (n=1). We did not identify any relevant published literature cases of *C. difficile* infection associated with vonoprazan use.

The Applicant identified 38 serious cases of *C. difficile* infections reported with vonoprazan use in the Takeda Global Safety Database. Their (Phathom) “review did not identify any index case of *C. difficile* associated with the use of vonoprazan.” They noted that the majority of cases are confounded by either use of other medications known to be independently associated with *C. difficile* (e.g., antibiotics) or confounded by underlying comorbidities. Furthermore, they state that, “Based on data from the clinical program and postmarketing reports, the risk of *C. difficile* enteric infection with vonoprazan treatment appears to be very low. Nonetheless, since this is an identified risk associated with other acid-suppressing agents, *C. difficile* is included in the Warnings and Precautions section of the label.”

Reviewer comment: We did not identify postmarketing cases in which vonoprazan by itself was plausibly associated with the development of C. difficile infection. However, similarly to the Applicant, we did find cases in which vonoprazan was used in combination with antibiotics prior to the development of C. difficile infection. We agree with the current labeling of C. difficile infection in the WARNINGS AND PRECAUTIONS section of the Voquezna product labeling based on the potential risk with other acid-suppressing medications (i.e., PPIs) and with coadministration of antibiotics.

3.6 VITAMIN B₁₂ DEFICIENCY

Vitamin B₁₂ deficiency is included in the WARNINGS AND PRECAUTIONS section of PPI labeling and is listed in the ADVERSE REACTIONS *Postmarketing Experience* section of the proposed Voquezna product labeling.

We retrieved zero FAERS reports^o and zero published literature cases describing vitamin B₁₂ deficiency associated with vonoprazan use.

The Applicant provided four Japanese postmarketing cases of vitamin B₁₂ deficiency with vonoprazan in their IR response. They noted that two of four cases had insufficient information to provide an assessment and two other cases were confounded by previous history of gastrectomy and atrophic gastritis. The four cases are summarized below.

^m Search using the High-Level Term Clostridia infections retrieved the following six FAERS case numbers: 15486152, 16718492, 17161901, 17554306, 19997886, 20307333.

ⁿ FAERS case #16718492 contained limited information but reported the patient was hospitalized with a urinary tract infection prior to the development of *C. difficile* infection; we presume the patient was treated with antibiotics, although not explicitly mentioned.

^o PTs for FAERS report identification: Anaemia vitamin B12 deficiency, Neuropathy vitamin B12 deficiency, Vitamin B12 abnormal, Vitamin B12 absorption test abnormal, Vitamin B12 decreased, Vitamin B12 deficiency, Anaemia megaloblastic.

Case 1: An 88-year-old female on galantamine for Alzheimer's disease for an unknown duration and vonoprazan for 217 days (20 mg daily for 63 days followed by 10 mg daily for 154 days) presented to the hospital; laboratory tests revealed hemoglobin 7, mean corpuscular volume (MCV) 114, and platelet count of 173,000 (units not reported). The patient declined examination for the cause of anemia. She underwent laboratory testing 182 days later; hemoglobin decreased slightly to 5.9, MCV was 124, and platelet count decreased to 106,000. Her labs were drawn again 99 days later (hemoglobin 5.5, MCV 131, platelet count 119,000). She was noted to have exertional dyspnea and lower leg edema and was treated with furosemide 20 mg/day. Another 19 days later, she was hospitalized. Her vitamin B₁ was 12 ng/mL, vitamin B₁₂ was 52 pg/mL, and folic acid was 1.9 ng/mL; pernicious anemia was suspected. Endoscopy revealed atrophy predominantly in the gastric fundus and body and she was diagnosis with type A gastritis. She was treated with intramuscular (IM) vitamin B₁₂ and supplemented with vitamin B₁ and folic acid. The next day, vonoprazan was discontinued. Her hemoglobin improved 19 days later from 4.5 to 6 and platelet count improved from 129,000 to 360,000. The next day, she was given IM mecobalamin. She was discharged 4 days later and thrombocytopenia and macrocytic anemia had resolved.

Case 2: A female of unknown age with an unknown medical history experienced vitamin B₁₂ deficiency sometime after starting vonoprazan 20 mg for an unknown indication. Treatment for the event, clinical course, and the event outcome were unknown. Concomitant medications were unknown.

Case 3: A 77-year-old female who had undergone gastrectomy at an unknown time was taking vonoprazan 20 mg daily for an unknown indication and developed anemia-like symptoms at an unknown time. "She seemed to have pancytopenia and her laboratory values were generally decreasing. Her physician considered the condition as anemia due to vitamin B₁₂ deficiency because she had undergone gastrectomy. The outcomes were unknown."

Case 4: A 71-year-old female experienced anemia with a hemoglobin of 9 (units not reported) and vitamin B₁₂ deficiency an unknown time after starting vonoprazan 10 mg daily. Concomitant medication was mecobalamin. The patient was treated with mecobalamin. Vonoprazan was continued and the outcome of the events was unknown.

Reviewer comment: We agree with the Applicant that two cases are unassessable (case 2 and 4) because of lack of clinical detail and that one case is unlikely/unassessable (case 3) because of history of gastrectomy and lack of other clinical detail.

Case 1 contains the most robust clinical detail, but at baseline, the patient was at risk for vitamin B₁₂ deficiency as she is elderly with atrophic gastritis; it is also important to note she presented with thiamine and mild folic acid deficiency. It is biologically plausible that vonoprazan could have contributed to the adverse event because inhibition of gastric acid secretion could theoretically promote malabsorption of cobalamin by multiple mechanisms, such as impairing extraction from dietary protein.¹⁹ We are unable to determine vonoprazan's role in the event because she improved after vonoprazan discontinuation and drug treatment and she was not rechallenged with the product.

Although there are a limited number of well-documented cases, we think it is reasonable to elevate this reaction to the WARNINGS AND PRECAUTIONS section for consistency with PPI labeling and a plausible mechanism for the reaction.

3.7 HYPOMAGNESEMIA

Hypomagnesemia and other related electrolyte abnormalities (e.g., hypocalcemia, hypokalemia) are included in the WARNINGS AND PRECAUTIONS section of PPI product labeling, but only the term hypomagnesemia is included in ADVERSE REACTIONS *Postmarketing Experience* of the proposed Voquezna label. The Voquezna Applicant's position is that, "The lack of studies establishing a definitive cause and effect relationship between acid suppressing therapies and hypomagnesemia, as well as data from the clinical program and postmarketing reports, suggests the risk of developing hypomagnesemia is very low. The proposed label includes hypomagnesemia in the postmarketing adverse drug reactions section."^{p,3}

We retrieved six FAERS reports^q of hypomagnesemia with or without other electrolyte abnormalities during use of vonoprazan. Of the six reports, two were duplicates. Of the remaining four reports, all were published in the medical literature; three^r were deemed possibly related to vonoprazan use and one²⁰ was deemed unlikely related. Our literature search did not retrieve any additional cases; therefore, the three total cases are summarized below.

FAERS Case #19725016/19902587, Other Important Medical Event, JPN, 2021:

This published case report⁶ describes a 71-year-old female admitted for the treatment of diffuse large B-cell lymphoma of the ileum; treatment consisted of pirarubicin, cyclophosphamide, vincristine, prednisone, and rituximab. She was taking lansoprazole to prevent gastric mucosal injury but was switched to vonoprazan due to epigastric discomfort and heartburn. Three weeks later, she visited an outpatient clinic for poor physical condition and experienced a convulsive seizure with loss of consciousness. She was admitted to the hospital for investigation of the cause. Laboratory tests revealed hypomagnesemia (0.4 mg/dL) and hypokalemia (2.8 me/L) as well as slightly elevated bilirubin (1.3 mg/dL) and transaminase levels (AST 51 U/L, ALT 70 U/L).^s Hypomagnesemia was considered the cause of the seizure and magnesium 40 mEq was given intravenously. The next day, her magnesium level improved to 2.2 mg/dL, and magnesium therapy was stopped. However, her magnesium level decreased gradually; on hospital day 7, it was approximately 1 mg/dL. Vonoprazan was discontinued. By hospital day 10, her magnesium level improved to 2.1 mg/dL. She was discharged after receiving her chemotherapy regimen for lymphoma. She was switched to famotidine and continued to receive outpatient treatment for lymphoma without recurrence of hypomagnesemia.

Reviewer comment: We deemed this case of hypomagnesemia and hypokalemia as possibly related to vonoprazan use because of 1) the close temporal relationship (3 weeks), 2) recurrent hypomagnesemia despite magnesium supplementation until vonoprazan was discontinued, and 3)

^p Per page 195 of the Integrated Summary of Safety.

^q PTs for FAERS report identification: Hypomagnesaemia, Blood magnesium abnormal, Blood magnesium decreased, Magnesium deficiency, Hypocalcaemia, Adjusted calcium decreased, Blood calcium abnormal, Blood calcium decreased, Calcium deficiency, Calcium ionised abnormal, Calcium ionised decreased, Tetany, Seizure.

^r The two full literature publications (Aiba and Okamoto) were reviewed by the Applicant in their ISS analysis.

^s Normal ranges were not provided.

lack of other reported obvious causes (chemotherapy was continued without recurrent hypomagnesemia). Notably, the patient developed severe hypomagnesemia (serum magnesium 0.4 mg/dL) and seizures.

FAERS Case #21106338, Hospitalization/Other Important Medical Event, JPN, 2022:

This published case report⁷ describes a 66-year-old male with a history of myocardial infarction and cerebral infarction admitted to the hospital because of disturbances in gait and consciousness. Approximately 2 years prior, he underwent endovascular aortic repair for abdominal aortic aneurysm; at that time, he was taking a PPI, which was changed to vonoprazan. Approximately 4 months after the procedure, he experienced a sudden clonic convulsion diagnosed as symptomatic epilepsy associated with old cerebral infarction and treated with levetiracetam. At that time, his serum calcium was slightly low at 7.2 mg/dL (albumin-corrected calcium 7.5 mg/dL), but his magnesium level was not measured.

Two months before his current admission, he had diarrhea and appetite loss; approximately 2 weeks later (43 days before the current admission), he went to the emergency department for convulsions and altered consciousness. His serum magnesium was 0.4 mg/dL, potassium was 2.66 mEq/L, and albumin-corrected calcium was 6.9 mg/dL. His symptoms improved spontaneously, and he left the hospital.

He gradually became unable to walk, and was ultimately admitted to the hospital with disturbance in consciousness. He was taking vonoprazan, levetiracetam, clopidogrel, diltiazem, telmisartan, amlodipine, nicorandil, bisoprolol, and isosorbide dinitrate. Electroencephalogram and head computed tomography scan were normal, however, serum electrolytes were abnormal. His serum magnesium was 0.2 mg/dL, potassium was 3 mEq/L, and albumin-corrected calcium was 5.7 mg/dL. Serum intact-parathyroid hormone, 1,25-dihydroxyvitamin D, and calcitonin levels were all within normal ranges. Intravenous magnesium and oral calcium were given, and his serum magnesium increased to 2 mg/dL of day 2 of admission with improvement in consciousness. His serum calcium levels improved steadily, but his magnesium levels rapidly declined once intravenous administration was discontinued, even though he had a sufficient intake after hospitalization. It was suspected that he had experienced magnesium malabsorption induced by long-term treatment with an antacid drug and vonoprazan, which had been used for over 2 years; therefore, vonoprazan was stopped on day 5 of hospital admission. Although temporary intravenous administration of magnesium was needed again as serum magnesium decreased to 1.1 mg/dL on the day 10 of admission, his serum magnesium level increased naturally to 1.6 mg/dL on day 20 after discontinuation of vonoprazan. An H₂ antagonist was started instead of vonoprazan on the same day, and serum magnesium has not decreased again.

Reviewer comment: We deemed this case of hypomagnesemia, hypokalemia, and hypocalcemia resulting in altered consciousness as possibly related to vonoprazan use. It is difficult to establish the exact temporal relationship between the initiation of vonoprazan and the development of electrolyte abnormalities. The patient's first seizure episode occurred approximately 4 months after starting vonoprazan, but a serum magnesium level was not drawn at that time; the first magnesium level was drawn approximately 2 years after vonoprazan initiation when the patient was experiencing diarrhea and loss of appetite, which are alternative explanations for the abnormal lab value. However, the patient's most recent hospitalization for

disturbance of consciousness and associated electrolyte disorders was possibly associated with vonoprazan use because of the lack of other alternative explanations and recurrent hypomagnesemia despite magnesium supplementation until vonoprazan was discontinued for a period of time. It is important to note that the patient had severe hypomagnesemia (serum magnesium 0.2 mg/dL) and disturbances in consciousness and gait.

FAERS Case #19928990, Hospitalization, JPN, 2021:

This is a literature abstract²¹ describing a 72-year-old female receiving afatinib for lung adenocarcinoma (for approximately 1 year), vonoprazan (unknown duration), and aspirin for history of cerebral infarction who was hospitalized for nausea, decreased appetite, hypokalemia, and hypocalcemia. Queasy feeling began 1 month earlier, which gradually increased and led to decreased appetite. Afatinib was suspected as the cause of nausea and decreased appetite, therefore, it was temporarily discontinued. Hypokalemia and hypocalcemia were noted on admission, however, their causes were unknown. Potassium and calcium replacement were given without improvement of hypokalemia and hypocalcemia, and numbness and pain of lower extremities occurred as well as difficulty in swallowing. The patient also experienced hypomagnesaemia, which was suspected as the cause of hypokalemia and hypocalcemia. Magnesium replacement resulted in a rapid improvement of the neuromuscular manifestation. Vonoprazan was suspected as the cause of hypomagnesemia, therefore, it was switched to an H₂ blocker. Concomitant hyperthyroidism was also suspected; a diagnosis of destructive thyroiditis and low T3 syndrome was made upon a detailed examination, and iodine restriction was performed. On an unspecified date, the patient recovered from hypomagnesemia (without noted recurrence), hypokalemia, and hypocalcemia.

Reviewer comment: We were unable to retrieve this published literature abstract, therefore, we used only information available in the FAERS case. We note that the case was difficult to interpret as specific dates of drug administration and adverse event occurrence were missing, specific laboratory values were omitted, and vonoprazan was incorrectly referred to as a PPI. Despite these limitations, we cannot fully exclude the role of vonoprazan in this case and deem it a possible cause of the electrolyte abnormalities. The patient's poor appetite secondary to chemotherapy may provide an alternative explanation for or may have contributed to the electrolyte abnormalities. However, despite electrolyte supplementation, the patient did not fully recover until vonoprazan discontinuation. The reporter also describes hyperthyroidism as a suspected cause of the hypomagnesemia; although changes in thyroid function may be associated with alterations in serum electrolytes, we did not find strong data to support the reporter's hypothesis.

Overall, based on the seriousness of the cases, hypomagnesemia should be elevated to the WARNINGS AND PRECAUTIONS section of the Voquezna product labeling. In addition, other electrolyte abnormalities, such as hypokalemia and hypocalcemia, should be added to the new WARNINGS AND PRECAUTIONS subsection and ADVERSE REACTIONS Postmarketing Experience. This labeling would also be consistent with PPI product labeling.

3.8 FUNDIC GLAND POLYPS

The development of fundic gland polyps is labeled in the WARNINGS AND PRECAUTIONS section of both approved PPI product labeling and the proposed Voquezna product labeling.

We retrieved seven FAERS reports[†] with the PT Gastric polyps, of which all were duplicates of a single published case report (51-year-old female).²² Our literature search identified one additional relevant published case report (78-year-old female).²³ The two published case reports are summarized below.^{22,23}

The first case report²² describes a 51-year-old female with multicentric Castleman's disease who was initiated on PPI therapy; at the time of PPI initiation, esophagogastroduodenoscopy (EGD) revealed no polyps in the stomach. She took continuous PPI therapy, which consisted of lansoprazole 15 mg daily for approximately 4 years, followed by esomeprazole 20 mg daily for approximately 4 years, followed by vonoprazan 20 mg daily for approximately 2-3 months. After being on acid-suppression therapy for approximately 8 years, endoscopic findings showed no atrophy and no intestinal metaplasia in her stomach, but multiple fundic gland polyps were identified in the stomach. A biopsy of a pedunculated polyp measuring 10 millimeters in diameter at the greater curvature of the middle gastric body demonstrated well-differentiated tubular adenocarcinoma.

The second case report²³ describes a 78-year-old Japanese female with rheumatoid arthritis, treated with salazosulfapyridine and prednisolone, and hepatitis B "e" antigen-negative chronic infection who took omeprazole for 13 years followed by vonoprazan for 8 months. An EGD revealed large erythematous polyps considered to be hyperplastic polyps, swollen whitish polyps considered to be fundic gland polyps, and multiple white flat lesions. Vonoprazan was switched to famotidine and an EGD performed 10 months later showed regression of both hyperplastic and fundic gland polyps. The sizes of the hyperplastic polyps further decreased 22 months after vonoprazan cessation, but the fundic gland polyps remained unchanged.

Reviewer comment: Long-term PPI therapy in both cases likely contributed to the initial development of fundic gland polyps. However, it is possible vonoprazan contributed to the ongoing presence of fundic gland polyps due to its similar mechanism of action to PPIs. This theory is supported by the second case, in which the polyps receded in size after vonoprazan was switched to a histamine-2 receptor blocker. Unfortunately, neither case documents serial EGDs during both PPI and vonoprazan use to better understand the timeline of the events in association with the therapies.

We agree with labeling the risk of fundic gland polyps in the WARNINGS AND PRECAUTIONS section of the Voquezna product labeling.

3.9 HYPERSENSITIVITY, INCLUDING ANAPHYLAXIS, DRUG ERUPTION, AND ERYTHEMA MULTIFORME

The proposed Voquezna product labeling contains a CONTRAINDICATION in patients with a known hypersensitivity to the product or any component of the product. Additionally, anaphylactic shock (*Postmarketing Experience*), drug hypersensitivity (*Clinical Trials Experience*), severe cutaneous adverse reactions (WARNINGS AND PRECAUTIONS,

[†] FAERS Case # 16630806, 16709649, 16729895, 16737719, 16959736, 17091750, 17096405.

Postmarketing Experience), erythema multiforme (*Postmarketing Experience*), and drug eruption (*Postmarketing Experience*) are listed in the proposed Voquezna product labeling.

We retrieved two FAERS reports with SMQ *Anaphylactic reaction (narrow)* and *Anaphylactic/anaphylactoid shock conditions (narrow)*; one report described anaphylaxis likely related to piperacillin-tazobactam administration (unlikely related to vonoprazan) and one report described hemorrhagic shock (not adverse event of interest and unlikely related to vonoprazan).

We retrieved 29 reports with the PT Erythema multiforme reported with vonoprazan use in the FAERS database. We did not deem any of the 29 reports to be plausibly associated with vonoprazan use; the reports were either duplicates or contained other medications that were either deemed to be the culprit (e.g., amoxicillin, clarithromycin) or confounded the causal assessment to vonoprazan (e.g., patient received multiple medications at the same time without sufficient information to assess the causal relationship to the event).

We retrieved 18 reports with the PT Drug eruption reported with vonoprazan use in the FAERS database. We did not deem any of the 18 reports to be plausibly associated with vonoprazan use; the reports were either duplicates or contained other medications that were either deemed to be the culprit (e.g., molnupiravir, isoniazid) or confounded the causal assessment to vonoprazan (e.g., patient received antibiotics at the same time without sufficient information to assess the causal relationship to the event).

Our literature search did not retrieve any relevant cases of hypersensitivity events plausibly related to vonoprazan use.

The Applicant provided the following five cases of hypersensitivity adverse events in their IR response: anaphylactic shock (1), anaphylactoid reaction/dermatitis exfoliative generalized/drug eruption (1), erythema multiforme (1), Stevens-Johnson syndrome (1), and toxic skin eruption (1). The cases are summarized below:

Anaphylactic shock: A surgeon reported that a 44-year-old male who was given his first dose of vonoprazan for epigastric pain developed nausea, generalized itching, and sweating within 10 to 15 minutes and was taken to the emergency room. He developed facial pallor, tachycardia, and hypotension and a diagnosis of anaphylactic shock was made. He was treated with steroids and epinephrine and recovered fully. The Applicant stated that, “Based on temporal relationship and lack of confounders, causal relationship could not be ruled out.”

Reviewer comment: We agree with the Applicant’s assessment that this case of anaphylactic shock is possibly associated with vonoprazan use, supporting the proposed contraindication for use and corresponding labeling in Postmarketing Experience. The patient’s signs and symptoms met Sampson criteria²⁴ for anaphylaxis requiring treatment with epinephrine and steroids. Additionally, no other cause for the event was identified.

Anaphylactoid reaction (contained co-reported PTs of Dermatitis exfoliative generalized and Drug eruption): A pharmacist reported that a 33-year-old male receiving acotiamide hydrochloride for an unknown duration was switched to vonoprazan from esomeprazole, and 30

to 60 minutes later, he presented with redness over his entire body and pharyngeal pain. He went to the emergency clinic. Generalized drug eruption and anaphylaxis (anaphylactoid symptoms) were suspected, and he was urgently hospitalized. Marked homogenous redness was observed over the entire body, including his head, neck, limbs, and trunk. The redness was accompanied by mild edematous changes. Blanching of the redness on pressure was observed, but there were no wheals. A diagnosis of erythroderma was made. He also presented with painful oral lesion (diffuse red swelling of the oral mucosa within the visible area), fever, and malaise. Vonoprazan fumarate was discontinued, and he received a dose of IV glycyrrhizin/glycine/cysteine and a dose of IV hydrocortisone sodium succinate 500 mg. Treatment with fexofenadine 60 mg and esomeprazole 20 mg was started. His blood sample was submitted for a lymphocyte transformation test with vonoprazan fumarate, which was later positive. Treatment with steroids was continued and symptoms resolved over the next few days.

Reviewer comment: This case does not meet Sampson criteria²⁴ for anaphylaxis but does represent a hypersensitivity reaction likely related to vonoprazan based on the temporal relationship.

Erythema multiforme: A physician and dermatologist reported that a 58-year-old female with GERD, who was treated with rebamipide and vonoprazan 20 mg daily for 9 days, developed fever and erythema. Both products were discontinued. The next day, she presented to the dermatology department with a fever of 39°C, generalized erythema, and bulbar conjunctival hyperemia. She was admitted to the hospital for suspected drug eruption and treated with a prednisolone taper. A lymphocyte transformation test gave a false-positive result for vonoprazan. Histopathologic exam findings were indicative of erythema multiforme, consisting of an area of liquefaction degeneration at the dermoepidermal junction and infiltration of inflammatory cells, such as eosinophils, around the vessels of the papillary layer. She was discharged from the hospital after 12 days, and the event resolved 7 days later. The dermatologist assessed the relationship of the event to rebamipide as unlikely because the patient has received the product before without problem.

Reviewer comment: Rebamipide is a mucoprotective drug that induces prostaglandins, resulting in increased blood flow to the gastric mucosa, mucous secretion, and enhanced mucosal defense. It also scavenges free radicals and inhibits inflammatory reactions.²⁵ Hypersensitivity reactions such as urticaria, rash, itching, and eczema are known adverse reactions for rebamipide. Although we could not find specific information related to risk of erythema multiforme with rebamipide, a publication detailing data mining of the Korea Adverse Event Reporting System (KAERS) database (KIDS-KD) to detect new safety signals with rebamipide did not mention erythema multiforme.

We cannot rule out the role of either vonoprazan or rebamipide in the development of erythema multiforme in this case because the patient was treated with both medications for the same time period. The dermatologist reporter noted that the patient previously received rebamipide without problem, although, we do not know the prior duration of use of this product; this information suggests vonoprazan may be the more likely cause of the events. Unfortunately, the lymphocyte transformation test results do not aid in determining the cause of the event in this case.

SJS: Two physicians from the same institution reported that a 58-year-old female developed SJS 9 days after starting vonoprazan 10 mg daily for post-treatment of endoscopic submucosal dissection for early gastric cancer. Vonoprazan was discontinued 8 days later. Nine days later, she was referred to the dermatology department of another hospital for the skin disorder. Sometime within the next month, she was discharged with recovery. The company commented that, “the patient took no other drug other than vonoprazan fumarate, the event seems to have been causally related to this drug.”

Reviewer comment: This case contains limited information to support the diagnosis of SJS, but was reported by two physicians from the same institution.

Toxic skin eruption (non-serious): A physician reported that a 40-year-old male experienced toxicoderma on the same day he started taking vonoprazan 10 mg daily for reflux esophagitis. No concomitant medication was taken. Vonoprazan was discontinued the same day, he was treated with epinastine, and the event resolved 6 days later.

Reviewer comment: Based on the cases provided by the Applicant, we agree with the proposed Voquezna product labeling pertaining to hypersensitivity reactions.

3.10 GASTRIC ADENOCARCINOMA

Gastric adenocarcinoma is not listed as an adverse reaction with vonoprazan in the proposed Voquezna product labeling. Presence of gastric malignancy is contained in the WARNINGS AND PRECAUTIONS section of the proposed Voquezna product labeling and PPI labeling; this section discusses that symptomatic response to vonoprazan or PPI therapy does not preclude the presence of gastric malignancy.

Our medical literature search retrieved one case report⁸ describing a 51-year-old male diagnosed with biopsy-confirmed foveolar-type gastric adenocarcinoma 156 weeks after starting maintenance therapy with vonoprazan 10 mg daily. EGD “revealed an approximately 5-mm-sized reddish polyp with a raspberry-like morphology in the anterior wall of the upper body of the stomach... This lesion was different from the FGPs,…” Another approximately 4-mm-sized foveolar-type gastric adenocarcinoma was also detected at the posterior wall of the middle body of the stomach. He was first started on vonoprazan 20 mg daily for 4 weeks for reflux esophagitis diagnosed by endoscopy; gastric adenocarcinoma was not observed at that time, but he was noted to have small fundic gland polyps in the gastric body and fornix.

This case report originated from an ongoing phase 4 study (Vonoprazan-4003, VISION Study) which aims to investigate long-term safety of vonoprazan in comparison with lansoprazole as maintenance treatment in subjects with EE.³ The Applicant is aware of this case and included it in their comprehensive review of all cumulative cases reporting neuroendocrine or gastric tumors (from the clinical program and postmarketing reports);^u they determined the risk to be very low and consistent with other acid suppressing therapy and have included serum gastrin effects and ECL cell effects in the clinical pharmacology section of Voquezna product labeling.

^u Page 180 of Integrated Summary of Safety.

Of note, no treatment-emergent adverse events (TEAEs) associated with gastric cancer were identified using the Gastric Neoplasms Malignant MedDRA HLT from the EE healing studies pool by the Applicant, but two events were considered related to study drug by the investigator (but not Applicant) in the all-subjects-pool from the maintenance of EE studies pool.^v

Reviewer comment: This single case is not sufficient to warrant labeling at this time unless additional evidence exists from clinical trials.

3.11 QT PROLONGATION

With respect to QT prolongation, the proposed Voquezna product labeling contains the following:

- QT prolongation is listed in the ADVERSE REACTIONS Clinical Trials Experience section under less common adverse reactions occurring in <2% of patients with *Voquezna Triple Pak* due to the clarithromycin component.
- The PHARMCODYNAMICS *Cardiac Electrophysiology* section states, “At a dose 6 times the maximum recommended dose, vonoprazan does not prolong the QT interval to any clinically relevant extent.”

Our FAERS search^w and medical literature search retrieved one case report describing a 67-year-old male with hypertension, hyperlipidemia, and pruritis dermatitis taking lisinopril 10 mg daily, pravastatin 10 mg daily, and levocetirizine 5 mg daily. He was started on vonoprazan 20 mg daily for treatment of a gastric ulcer. A follow-up electrocardiogram (ECG) performed 4 months later showed QT prolongation, which was not observed before vonoprazan initiation. He had no evidence of electrolyte abnormalities and was switched to famotidine because of suspected drug-induced QT prolongation. ECG performed 1 week later showed improvement in QT interval.

Reviewer comment: Vonoprazan by itself has not been shown to prolong the QT interval at a dose 6 times the maximum recommended dose; a thorough QT study reviewed prior to approval of Voquezna Dual and Triple Pak by the Interdisciplinary Review Team for Cardiac Safety Studies showed no significant effect on QTcF prolongation.

A major limitation of this published case is that the authors do not provide the actual QT intervals to understand the extent of the event or confirm the findings. The authors only provide poor quality images of ECG tracings. A Cardiologist in DPV-I reviewed the images and stated they are not adequate to measure a QT interval or to calculate a corrected QT (QTc) interval. The ST and T wave morphology is different in tracing A (while on vonoprazan) as compared with tracings B or C, so it may be possible that the QTc interval could be prolonged. However, the patient’s heart rate could also be a factor with regard to measuring/calculation QTc, and the patient’s heart rate is faster in tracing A, than in tracing B or C.

^v Page 168 of Integrated Summary of Safety.

^w Our FAERS search retrieved five reports with the PTs Electrocardiogram QT prolonged and Long QT syndrome. Of the five reports, three did not describe QT prolongation with vonoprazan and two described the same published literature report identified in our literature search (FAERS Case # 20414969 and 20433305).

The authors speculate that the vonoprazan plasma concentration was increased with concomitant use of levocetirizine as both drugs are metabolized by CYP3A4 (i.e., CYP3A4 substrates). However, they do not have any data to support this mechanism and it seems unlikely to result in a considerable change in vonoprazan serum levels. Also, per levocetirizine product labeling, it has not been shown to demonstrate an effect on the QTc interval.²⁶

This single case report with poor quality clinical data is not sufficient to support changes to vonoprazan product labeling at this time.

3.12 ENDOSCOPIC/HISTOPATHOLOGIC FINDINGS

From our medical literature search, we identified multiple publications^{9, 10, 11, 12, 13, 14} describing patients who had endoscopic and histopathological evidence of one or more of the following during vonoprazan treatment: gastric erythema, parietal cell protrusions (PCP), vacuolar degeneration of parietal cells, oxyntic gland dilatation (OGD), inflammatory cell infiltration, and white globe appearance (WGA). See **Table 4** below for select clinical details from the 12 individual cases from the publications. Of the 12 cases, 9 described the endoscopic with or without histopathological findings after discontinuation of vonoprazan. Of note, no cases described clinical symptoms associated with these endoscopic and histopathological changes.

Reviewer comment: These findings are consistent with the underlying mechanism of vonoprazan and serum gastrin effects. As no clinical sequelae or symptoms associated with these findings were reported, further discussion of these endoscopic and histopathologic findings in Voquezna product labeling are not warranted at this time.

Reference/ Case #	Age (years)/ Sex	<i>H.</i> <i>pylori</i> status	Vonoprazan dose (mg)/ indication	Time after vonoprazan initiation	Endoscopic Findings	Histopathology Findings	Findings After Dechallenge*
Kubo 2020 ⁹ / Case 1	76/M	Previously infected	20/ gastric ulcer	5 months	Linear redness in greater curvature of middle gastric body	Inflammatory cell infiltration, PCP, OGD	At 12 months, redness resolved; change in pathological findings NR
Kubo 2020 ⁹ / Case 2	88/M	Previously infected	20/ post-ESD ulcer	4 months	Spotty redness in greater curvature of middle gastric body	Inflammatory cell infiltration, PCP, OGD	At 3 months, redness resolved; change in pathological findings NR
Kubo 2020 ⁹ / Case 3	73/M	Previously infected	20/ post-argon plasma coagulation ulcer	2 months	Spotty redness in greater curvature of middle gastric body	Inflammatory cell infiltration, PCP	At 3 months, redness and inflammatory cell infiltration resolved, no change in PCP
Kubo 2020 ⁹ / Case 4	79/F	Previously infected	20/ post-ESD ulcer	6 months	Spotty redness in greater curvature of	Inflammatory cell infiltration, PCP	At 3 months, redness resolved; change

Table 4. Select Case Details from Literature Publications Describing Endoscopic and Histopathological Changes Possibly Associated With Vonoprazan Use (n=12)

Reference/ Case #	Age (years)/ Sex	<i>H. pylori</i> status	Vonoprazan dose (mg)/ indication	Time after vonoprazan initiation	Endoscopic Findings	Histopathology Findings	Findings After Dechallenge*
					middle gastric body		in pathological findings NR
Kubo 2021 ¹⁰ / Case 1	76/F	No history of prior infection	20/ GERD	29 months	Spotty and linear redness in greater curvature of gastric body	Focal hemorrhage, slight congestion, mild inflammatory cell infiltration, PCP, vacuolar degeneration of parietal cells	At 1 and 3 months, redness diminished or disappeared and pathological findings improved
Kubo 2021 ¹⁰ / Case 2	80/F	No history of prior infection	20/ epigastric pain	20 months	Spotty and linear redness in greater curvature of gastric body	Focal hemorrhage and congestion beneath the basement membrane, mild inflammatory cell infiltration, PCP, OGD	At 5 months, redness resolved, improvement in hemorrhage and congestion but no change in other findings
Kubo 2021 ¹⁰ / Case 3	88/M	Previously infected	20/ gastric ulcer	1 month	Spotty and linear redness in greater curvature of gastric body	Focal hemorrhage, congestion, mild inflammatory cell infiltration, PCP, vacuolar degeneration of parietal cells, OGD	At 2 months, redness resolved, improvement in hemorrhage, congestion, and vacuolar degeneration of parietal cells but no change in other findings
Kubo 2021 ¹⁰ / Case 4	83/M	Previously infected	20/ gastric ulcer	9 months	Spotty and linear redness in greater curvature of gastric body	Focal hemorrhage, congestion, marked inflammatory cell infiltration, PCP, OGD	At 3 months, redness resolved and improvement in previous pathological findings
Miyamoto ¹¹	43/M	No history of prior infection	10/ GERD	6 months	Gastric cracked mucosa	PCP, OGD	NR
Miwa ^{12,13} / Case 1	68/F	No history of prior infection	10/ GERD, esophageal stricture	12 months	WGA in all regions of the stomach except antrum	Glandular cystic dilatation, glands containing eosinophilic material, PCP, OGD	At 3 months, most of WGA lesions had disappeared, limited improvement in pathological findings
Miwa ¹³ / Case 2	65/M	Previously infected	10/ GERD	48 months	White spot lesion/WGA in lesser	cystic gland dilatation containing	NR

Table 4. Select Case Details from Literature Publications Describing Endoscopic and Histopathological Changes Possibly Associated With Vonoprazan Use (n=12)

Reference/ Case #	Age (years)/ Sex	<i>H.</i> <i>pylori</i> status	Vonoprazan dose (mg)/ indication	Time after vonoprazan initiation	Endoscopic Findings	Histopathology Findings	Findings After Dechallenge*
					curvature of stomach body	eosinophilic material, marked PCP and OGD	
Iwamuro ¹⁴	82/M	No history of prior infection	NR/ reflux esophagitis, dyspepsia	NR	White spots in fornix and body	Cystic dilation of gastric fundal gland, PCP	NR

*Nine of 12 cases described switching to esomeprazole upon vonoprazan discontinuation.
Abbreviations: M=male , PCP=parietal cell protrusions, OGD=oxyntic gland dilatation, NR=not reported, ESD=endoscopic submucosal dissection, F=female, WGA=white globe appearance

3.13 GASTROINTESTINAL CANDIDIASIS

The proposed Voquezna product labeling does not contain gastric or esophageal candidiasis, but contains vulvovaginal candidiasis in the ADVERSE REACTIONS *Clinical Trials Experience* with Voquezna in combination with antibiotics. PPI product labeling contains candidiasis in the ADVERSE REACTIONS *Clinical Trials Experience* section (in Prevacid label, listed as adverse experience occurring in less than 1% if patients or subjects who received the product in domestic trials).

Our medical literature search identified one case¹⁵ describing a 59-year-old male who developed multiple ulcers with white moss in the fornix and gastric body on EGD 4 months after switching from esomeprazole 20 mg daily to vonoprazan 20 mg daily for treatment of epigastric pain and nausea; EGD prior to switching to vonoprazan showed only ulcer scars in the stomach. The patient had type 2 diabetes and a history of *H. pylori* eradication 2 years prior.

We identified a FAERS case (Case # 15258854) coded with the PT Gastrointestinal candidiasis; this case, describing an 82-year-old male, contained limited information to confirm the diagnosis (report states patient experienced “suspected” stomach candidiasis sometime after starting vonoprazan) and association to vonoprazan use as the patient also received risedronate, a bisphosphonate which has been associated with postmarketing reports of gastric and duodenal ulcers.

We also identified one additional case from FAERS (Case # 18694356) coded with the PT Oesophageal candidiasis that was also published in the literature.²⁷ However, we deemed this case to have unlikely causality to vonoprazan because the patient was on immunosuppressive medications (prednisolone, abatacept) for treatment of rheumatoid arthritis and SSc in addition to vonoprazan for prophylaxis of steroid-induced gastric ulcers.

Reviewer comment: The cases of gastrointestinal candidiasis do not warrant labeling at this time because of the presence of potential contributors to the events (immunosuppressed status from diabetes, other medications).

4 DISCUSSION

In response to the consult from DG, we reviewed postmarketing reports in the FAERS database and medical literature for an association between select AESIs^x and vonoprazan use. In addition, we reviewed data submitted by the Applicant in response to an IR issued by FDA. We also performed a high-level analysis of FAERS and searched the medical literature for new potential safety signals. Only adverse events for which a labeling action are recommended are discussed below, however, please refer to **Section 3** for full details of the AESI and other safety signals analyses.

- We identified two cases of suspected DITP from the medical literature with possible causal association with vonoprazan use; both cases noted positive dechallenge to vonoprazan, although one case was also treated with a short course of steroids. We suggest addition of the term, thrombocytopenia, to the *Postmarketing Experience* section of Voquezna product labeling based on these few cases.
- We identified one well-documented case of vitamin B₁₂ deficiency possibly associated with vonoprazan use. Although the patient was elderly with atrophic gastritis, which represent risk factors for the event, vonoprazan could have contributed to the event particularly in a vulnerable patient. Inhibition of gastric acid secretion could theoretically promote malabsorption of cobalamin by multiple mechanisms and for consistency with PPI product labeling, we recommend elevating vitamin B₁₂ deficiency to the WARNINGS AND PRECAUTIONS section of the Voquezna product labeling.
- We identified three cases in which patients experienced hypomagnesemia and other related electrolyte abnormalities (hypokalemia n=3, hypocalcemia n=2) possibly associated with vonoprazan use. Although it is difficult to assess the response to dechallenge in these cases, we note that all three cases described resolution of the electrolyte abnormalities after electrolyte replacement and vonoprazan discontinuation; two cases explicitly mentioned that there was no further recurrence. Two cases were noteworthy as the patients presented with critically low magnesium levels (0.2-0.4 mg/dL) with clinically significant sequelae (seizures n=1, disturbances in gait/consciousness n=1). The remaining case was limited because the patient's actual electrolyte values were not reported, but the patient did experience neuromuscular manifestations with the reported electrolyte abnormalities. Based on the seriousness of the cases, hypomagnesemia should be elevated to the WARNINGS AND PRECAUTIONS section of the Voquezna product labeling. In addition, other electrolyte abnormalities, such as hypokalemia and hypocalcemia, should be added to the new WARNINGS AND PRECAUTIONS subsection and ADVERSE REACTIONS *Postmarketing Experience*. This labeling would also be consistent with PPI product labeling.

5 CONCLUSION

In conclusion, we find sufficient evidence from our review of postmarketing data to update the proposed Voquezna product labeling with respect to the safety issues of hypomagnesemia and other related electrolyte abnormalities, vitamin B₁₂ deficiency, and thrombocytopenia.

^x Hepatic dysfunction, cytopenias, bone fracture, lupus, C. difficile infection, vitamin B12 deficiency, hypomagnesemia, fundic gland polyps, hypersensitivity (including anaphylaxis, drug eruption, and erythema multiforme)

6 RECOMMENDATIONS

Based on this review, DPV-I recommends the following:

- Add 1) hypomagnesemia and other related electrolyte abnormalities and 2) vitamin B₁₂ deficiency to new WARNINGS AND PRECAUTIONS subsections.
- Add other related electrolyte abnormalities of hypokalemia and hypocalcemia to the ADVERSE REACTIONS *Postmarketing Experience* section.
- Add thrombocytopenia to the *Postmarketing Experience* section.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 APPENDIX B. HIGH-LEVEL ANALYSIS OF FAERS REPORTS FOR SIGNAL GENERATION

MedDRA PT	Number of FAERS Reports*	Labeled (Yes/No), Location† or Other Category
Erythema multiforme	29	Yes, AR; See Section 3.9
Drug interaction	27	Yes, DI, the mechanisms likely underlying the interactions are labeled for both vonoprazan and the other products (bosentan, ledipasvir and sofosbuvir, duloxetine); See Section 3.1 for the case involving bosentan.
Hepatic function abnormal	25	Yes, AR; See Section 3.1
Off label use	19	No, U
Rash	19	Yes, AR
Diarrhoea	18	Yes, AR
Drug eruption	18	Yes, AR; See Section 3.9

Table 5. Top 50 Most Frequently Reported MedDRA PTs With Vonoprazan Received by FDA Through September 26, 2022, Sorted by Decreasing Number of FAERS Reports per PT

Anaemia	16	No; See Section 3.2
Pyrexia	16	No, co-reported sign of other labeled adverse reaction (e.g., erythema multiforme)
Interstitial lung disease	14	No, U
Enterocolitis haemorrhagic	13	No, reported in combination with antibiotics for <i>H. pylori</i> eradication
Decreased appetite	12	No, U
Erythema	12	No, but erythema multiform is labeled in AR
Liver disorder	12	Yes, AR (labeled as liver function test abnormal); See Section 3.1
Stevens-Johnson syndrome	12	Yes, W/P; See Section 3.9 for a summary of one SJS case
Nausea	11	Yes, AR
Gastric ulcer	10	Yes, AR
Gastrointestinal haemorrhage	10	No, AltEx
Hypergastrinaemia	10	Yes, AltEx
Renal impairment	10	Yes, W/P (labeled as acute tubulointerstitial nephritis); no reports deemed plausibly associated to vonoprazan use—they contained confounders (e.g., chemotherapy, acute blood loss, pre-existing renal dysfunction) and some contained limited information for assessment
Vomiting	10	Yes, AR
Drug ineffective	9	No, U
Platelet count decreased	9	No; See Section 3.2
Cardiac failure	8	No, U
Cataract	8	No, U
Malaise	8	No, U
Visual impairment	8	No, U
Abdominal pain	7	Yes, AR
Altered state of consciousness	7	No, U
Blood pressure decreased	7	No, U
Gastric polyps	7	Yes, W/P

Table 5. Top 50 Most Frequently Reported MedDRA PTs With Vonoprazan Received by FDA Through September 26, 2022, Sorted by Decreasing Number of FAERS Reports per PT

Pancytopenia	7	No; See Section 3.2
Pruritis	7	No, U, may be co-reported symptom with rash
Rhabdomyolysis	7	No, U
Toxic epidermal necrolysis	7	Yes, W/P
Ascites	6	No, AltEx
Duodenal polyp	6	Yes, AR
Dyspepsia	6	Yes, AR
Fall	6	No, U
Hypersensitivity	6	Yes, C, AR
Loss of consciousness	6	Yes, labeled as syncope in AR
Oesophageal candidiasis	6	No, 3 unique reports in which patients were on other contributory medications (e.g., immunosuppressants, PPIs), some contained limited information for assessment; See Section 3.13
Acute kidney injury	5	Yes, W/P (labeled as acute tubulointerstitial nephritis); the reports are not informative as they describe acute kidney injury (AKI) associated with acute hemorrhage in patients taking anticoagulants (2), AKI from rhabdomyolysis deemed not plausibly associated with vonoprazan (2-duplicates), and chemotherapy use and anemia requiring transfusion prior to AKI (1)
Asthenia	5	No, U
COVID-19	5	No, U
Colitis microscopic	5	No, U (3 unique reports deemed unassessable)
Condition aggravated	5	No, U
Dementia	5	No, U
Dyspnoea	5	No, U
Febrile neutropenia	5	No; See Section 3.2

* A report can contain more than one MedDRA PT.

† If the event is included in multiple sections of labeling, only the section of highest importance is listed.

Table 5. Top 50 Most Frequently Reported MedDRA PTs With Vonoprazan Received by FDA Through September 26, 2022, Sorted by Decreasing Number of FAERS Reports per PT

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, Alt Ex = Alternative explanation (disease-related, indication-related, or concomitant medication-related), U = Uninformative

Table 6. Most Frequently Reported DMEs With Vonoprazan, Received by FDA Through September 26, 2022, Sorted by Decreasing Number of FAERS Reports per PT

DME MedDRA PT	Number of FAERS Reports*	Labeled (Yes/No), Location† or Other Category
Stevens-Johnson syndrome	12	Yes, W/P; See Section 3.9 for a summary of one SJS case
Pancytopenia	7	No; See Section 3.2
Rhabdomyolysis	7	No, U
Toxic epidermal necrolysis	7	Yes, W/P
Erythema	6	No, but erythema multiforme is labeled in AR
Pyrexia	6	No, co-reported sign of other labeled adverse reaction (e.g., erythema multiforme)
Rash	6	Yes, AR
Acute kidney injury	5	Yes, W/P (labeled as acute tubulointerstitial nephritis); the reports are not informative as they describe acute kidney injury (AKI) associated with acute hemorrhage in patients taking anticoagulants (2), AKI from rhabdomyolysis deemed not plausibly associated with vonoprazan (2-duplicates), and chemotherapy use and anemia requiring transfusion prior to AKI (1)
Hepatic function abnormal	5	Yes, AR; See Section 3.1
Agranulocytosis	4	No; See Section 3.2
Drug interaction	4	Yes, DI, the mechanisms likely underlying the interaction are labeled for both vonoprazan and the other products

		(bosentan, ledipasvir and sofosbuvir, duloxetine); See Section 3.1 for the case involving bosentan.
Drug reaction with eosinophilia and system symptoms	4	No, U; All reports describe concomitant use of antibiotics (3) or lamotrigine (1) and are deemed unlikely/unassessable in relation to vonoprazan use
Drug-induced liver injury	4	Yes, AR; See Section 3.1
Erythema multiforme	4	Yes, AR
Febrile neutropenia	4	No; See Section 3.2
Hypomagnesemia	4	Yes, AR; See Section 3.7
Oral pain	4	No, co-reported as symptom of other labeled adverse reaction (e.g., SJS)
Oropharyngeal pain	4	No, co-reported as symptom of other labeled adverse reaction (e.g., SJS)
Blood creatinine phosphokinase increased	3	No, U
Decreased appetite	3	No, U
Electrocardiogram QT prolonged	3	No; See Section 3.11
Gastrointestinal haemorrhage	3	No, AltEx
Liver disorder	3	Yes, AR (labeled as liver function test (b) (4)); See Section 3.1
Nausea	3	Yes, AR
Off label use	3	No, U
Oral mucosa erosion	3	No, co-reported as symptom of other labeled adverse reaction (e.g., SJS)
Renal failure	3	Yes, W/P (labeled as acute tubulointerstitial nephritis)
Seizure	3	No, co-reported with electrolyte abnormalities; See Section 3.7
Anaemia	2	No; See Section 3.2
Cellulitis	2	No, U
Chronic obstructive pulmonary disease	2	No, U
Condition aggravated	2	No, AltEx
Dyspnoea	2	No, U
Epigastric discomfort	2	Yes, AR
Epistaxis	2	No, U
Fatigue	2	No, U

Gastric ulcer	2	Yes, AR
Hepatic failure	2	Yes, AR; See Section 3.1
Hypocalcaemia	2	No; See Section 3.7
Loss of consciousness	2	No, but syncope labeled in AR
Malaise	2	No, U
Myelosuppression	2	No; See Section 3.2
Pneumonia staphylococcal	2	No, U
Product use issue	2	No, U
Pruritis	2	No, U
Renal impairment	2	Yes, W/P (labeled as acute tubulointerstitial nephritis)
Shock haemorrhagic	2	No, AltEx
Urine output decreased	2	No, but W/P (labeled as acute tubulointerstitial nephritis)
Abdominal distension	1	Yes, AR
Abdominal pain upper	1	Yes, AR
* A report can contain more than one MedDRA PT. † If the event is included in multiple sections of labeling, only the section of highest importance is listed. Abbreviations: DME = Designated Medical Event, MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, Alt Ex = Alternative explanation (disease-related, indication-related, or concomitant medication-related), U = Uninformative		

7.3 APPENDIX C. LIST OF OSE DESIGNATED MEDICAL EVENTS

System Organ Class	Preferred Terms (MedDRA version 25.0)
Blood and lymphatic system disorders	Agranulocytosis
	Aplastic anaemia
	Bone marrow failure
	Coombs negative haemolytic anaemia
	Coombs positive haemolytic anaemia
	Haemolytic anaemia
	Haemolytic uraemic syndrome
	Microangiopathic haemolytic anaemia
	Pancytopenia
	Thrombotic microangiopathy
	Thrombotic thrombocytopenic purpura
Cardiac disorders	Torsade de pointes
	Ventricular fibrillation
Ear and labyrinth disorders	Deafness
	Deafness bilateral
	Deafness neurosensory
	Deafness permanent
	Deafness transitory
	Deafness unilateral
	Ototoxicity
	Sudden hearing loss
Eye disorders	Blindness
	Blindness transient
	Blindness unilateral
	Optic ischaemic neuropathy
	Sudden visual loss

System Organ Class	Preferred Terms (MedDRA version 25.0)
	Toxic optic neuropathy
Gastrointestinal disorders	Haemorrhagic necrotic pancreatitis
	Pancreatitis haemorrhagic
	Pancreatitis necrotising
General disorders and administration site conditions	Sudden cardiac death
	Sudden death
Hepatobiliary disorders	Acute hepatic failure
	Drug-induced liver injury
	Hepatic failure
	Hepatic necrosis
	Hepatitis fulminant
Immune system disorders	Anaphylactic reaction
	Anaphylactic shock
	Anaphylactoid reaction
	Anaphylactoid shock
Infections and infestations	Progressive multifocal leukoencephalopathy
	Suspected transmission of an infectious agent via product
	Transmission of an infectious agent via product
Investigations	Electrocardiogram QT prolonged
Musculoskeletal and connective tissue disorders	Myopathy toxic
	Rhabdomyolysis
Nervous system disorders	Generalised tonic-clonic seizure
	Seizure
	Serotonin syndrome
	Status epilepticus
Product issues	Product compounding quality issue
	Product contamination
	Product contamination chemical
	Product contamination microbial

System Organ Class	Preferred Terms (MedDRA version 25.0)
	Product contamination physical
	Product sterility issue
Psychiatric disorders	Completed suicide
Renal and urinary disorders	Acute kidney injury
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis
	Drug reaction with eosinophilia and systemic symptoms
	Generalised bullous fixed drug eruption
	Severe cutaneous adverse reaction
	SJS-TEN overlap
	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
Surgical and medical procedures	Liver transplant

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 3, 2022
Requesting Office or Division: Division of Gastroenterology (DG)
Application Type and Number: NDA 215151
Product Name and Strength: Voquezna (vonoprazan) tablets, 10 mg and 20 mg
Applicant/Sponsor Name: Phathom Pharmaceuticals, Inc.
OSE RCM #: 2022-555-1
DMEPA 1 Safety Evaluator: Sherly Abraham, R.Ph.
DMEPA 1 Team Leader: Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 14, 2022 for Voquezna. The Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for Voquezna (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Our evaluation of the proposed Voquezna label and labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Table 1 for the Applicant. We ask that the Division convey Table 1 in its entirety to Phathom Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

^aAbraham, S. Label and Labeling Review for Voquezna (NDA 215151). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 31. RCM No.: 2022-555.

2.1 RECOMMENDATIONS FOR PHATHOM PHARMACEUTICALS, INC.

Table 1. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The Proprietary name and established names are not the most prominent information on the primary display panel.	Proprietary name and established name should be the most prominent information on the label in order to be in accordance with 21 CFR 201.10(g)(2).	Increase the prominence of the proprietary name and established name or decrease the font size of the strength statement. If prominence of the proprietary name is increased, ensure that the established name is at least half the size of the proprietary name as per 21 CFR 201.10(g)(2).

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/s/

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Division of Pediatric and Maternal Health Memorandum

Date: 10/19/22 **Date Consulted:** 5/5/22

From: Jane Liedtka, M.D., Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, Director, DPMH

To: Maureen Dewey, Regulatory Project Manager (RPM)
Division of Gastroenterology (DG)

Drug/NDA: Voquenza (vonoprazan), N 215151

Indication: Voquenza is a potassium-competitive acid blocker (PCAB) indicated for:

- Healing of all grades of erosive esophagitis (EE) and relief of heartburn.
- Maintenance of healing of all grades of EE and relief of heartburn.
- Treatment of Helicobacter pylori (H. pylori) infection.

Applicant: Phathom Pharmaceuticals

Subject: Pregnancy and Lactation Labeling [Original New Drug Application (NDA)]

Materials Reviewed:

- Applicant's submission dated 3/11/22
- DPMH review for (b) (4) Triple Pak and Dual Pak; NDAs 215152, 215153. Jane Liedtka, M.D. 3/24/22. DARRTS Reference ID # 4957884.¹

Consult Question: Review labeling.

¹DPMH review for (b) (4) Triple Pack and Dual Pak; NDAs 215152, 215153. Jane Liedtka, M.D. 3/24/22. DARRTS Reference ID # 4957884.

INTRODUCTION AND BACKGROUND

- On 3/11/22, Phathom Pharmaceuticals submitted original NDA 215151 for Voquezna (vonoprazan) to DG for the indications of healing of EE, maintenance of EE and *H. pylori* infection.
- On 5/5/22 DG consulted DPMH to assist with the proposed labeling language for Section 8 for NDA 215151.
- Phathom Pharmaceuticals had previously submitted two NDAs, 215152 (b) (4) Triple Pack (vonoprazan/amoxicillin/clarithromycin) and 215153 (b) (4) Dual Pack (vonoprazan/amoxicillin) to the division of anti-infectives (DAI) for the treatment of *H. pylori* infection. NDAs 215152 and 215153 were approved on 5/4/22. DPMH was consulted to assist with the proposed labeling language for Section 8 for these applications and archived a review in DARRTS on 3/24/22¹. The proprietary name of (b) (4) was denied after the DPMH review was archived in DARRTS. The proprietary name associated with the submission upon approval was VOQUEZNA.
- Vonoprazan belongs to a new class of acid-inhibitory agents called potassium-competitive acid blockers (PCAB). Vonoprazan had been approved as a stand-alone product in Japan since 2014 for *H. pylori*, peptic and duodenal ulcers and esophagitis, and as a combination product with antibiotics for *H. pylori* infection since 2016. There had been additional approvals in Asia and Latin America. According to the applicant, cumulatively over (b) (4) patients have been exposed to vonoprazan since 2014.
- The recommended adult oral dosage of Voquezna for healing of EE is vonoprazan 20 mg once daily, for (b) (4) 8 weeks. The recommended adult oral dosage of Voquezna for maintenance of EE is vonoprazan 10 mg once daily, for up to 6 months. See previous DPMH review¹ for dosing for *H. pylori*.

Table 1: Drug Characteristics²

	Vonoprazan
Half-life (steady state, twice daily dose)	6.8 hours
Molecular weight	461.5 Daltons
Protein-binding	85-88%

Source: Reviewer's Table

See previous DPMH review¹ for discussion of “H. Pylori Infection (HPI) and Pregnancy”, “Nonclinical Experience”, “Review of Pharmacovigilance Database (PVDB)”, “Applicant’s Review of Literature on Vonoprazan for Pregnancy, Lactation, Use in Females and Males of Reproductive Potential”, “DPMH’s Review of Literature on Vonoprazan for Pregnancy, Lactation and Use in Females and Males of Reproductive Potential”.

See Appendix A for relevant excerpts from “Current State of the Labeling” for VOQUEZNA Dual Pak from approved labeling dated 5/3/22.

² Approved Voquezna Dual Pak labeling dated 5/3/22.

DISCUSSION AND CONCLUSIONS FROM PREVIOUS DPMH REVIEW

Pregnancy

Vonoprazan

There are no human pregnancy outcome data for vonoprazan that were found in the published English language literature. The applicant's pharmacovigilance database (PVDB) information (from approvals outside the US) was limited by a high percentage of unknown outcomes. There were no signals of concern in the animal studies for pregnancy from vonoprazan products at relevant doses. See proposed labeling for recommended language.

H. Pylori occurs commonly in females of reproductive potential and treatment may be prescribed to pregnant women not yet aware of their pregnancy. Given the lack of information on use during pregnancy and the potential use of (b) (4) TRIPLE PAK and (b) (4) DUAL PAK in an at-risk population, DPMH recommends gathering additional pregnancy exposure data to assess the safety of vonoprazan-containing products use during pregnancy. A post-marketing requirement (PMR) for a pregnancy exposure registry and a postmarketing pregnancy study of a different design should be issued for vonoprazan-containing products.

Lactation

Vonoprazan

It is not known whether vonoprazan is present in human milk. There are no reports in the published literature or in the applicant's PVDB of human infant exposure via lactation. Vonoprazan is found in rat milk. Nonclinical studies in rats revealed "liver lesions" in rat pups exposed to vonoprazan only through lactation.

DPMH recommends a PMR for a "milk only" clinical lactation study to assess whether vonoprazan is present in clinically relevant quantities in human milk. If this is found to be the case, further lactation studies may be needed to assess vonoprazan levels in infants exposed to the product via lactation.

Females and Males of Reproductive Potential

Vonoprazan and amoxicillin did not have any worrisome animal findings with regard to effects on fertility. This reviewer did not find any additional information in the published human literature on this topic.

CURRENT REVIEW

Discussion and Conclusions

No new published literature regarding use of vonoprazan during Pregnancy, Lactation or use in Females and Males of Reproductive Potential were identified. Voquezna labeling will align with the vonoprazan component content in the approved VOQUEZNA Dual Pak and Triple Pak labeling.

Because the duration of therapy for Voquezna is longer than for the previously approved VOQUEZNA Dual Pak and Triple Pak indications ((b) (4) for VOQUEZNA's original

application indications versus up to 6 months for Voquenza for EE), it will not be feasible for patients to pump and discard during treatment and then resume lactation. Therefore, the recommended lactation labeling language will not state “pump and discard” but advise patients to “Do not breast feed during treatment”.

There are already existing post-marketing requirements (PMRs) for a pregnancy exposure registry and a postmarketing pregnancy study of a different design for vonoprazan-containing products issued at the time of VOQUEZNA approval. The sponsor should revise the current protocols for these 2 PMRs to add patients with erosive esophagitis who become pregnant during treatment with Voquenza to these studies.

There is already an existing PMR for a “milk only” clinical lactation study to assess whether vonoprazan is present in clinically relevant quantities in human milk.

Vonoprazan did not have any worrisome animal findings with regard to effects on fertility. This reviewer did not find any additional information in the published human literature on this topic. There is no need for pregnancy testing or contraception with use of Voquenza. Therefore, DPMH recommends omitting the subsection 8.3 “” from Voquenza labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2 and 17 of Voquenza(vonoprazan) labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Voquenza (vonoprazan) Pregnancy and Lactation Labeling



Appendix A: Relevant Excerpts from current approved VOQUEZNA TRIPLE PAK and DUAL PAK labeling, 5/3/2022

HIGHLIGHTS OF PRESCRIBING INFORMATION

VOQUEZNA TRIPLE PAK (vonoprazan tablets; amoxicillin capsules; clarithromycin tablets), co-packaged for oral use

VOQUEZNA DUAL PAK (vonoprazan tablets; amoxicillin capsules), co-packaged for oral use

Initial U.S. Approval: 2022

-----**USE IN SPECIFIC POPULATIONS**-----

- Lactation: Breastfeeding not recommended during treatment, but a lactating woman can pump and discard breast milk during treatment and for 2 days after VOQUEZNA TRIPLE PAK or VOQUEZNA DUAL PAK administration. (8.2)

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

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VOQUEZNA DUAL PAK

There are no adequate and well-controlled studies of VOQUEZNA DUAL PAK in pregnant women to evaluate for drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Individual Components of VOQUEZNA TRIPLE PAK and VOQUEZNA DUAL PAK

Vonoprazan:

Available data from pharmacovigilance reports with vonoprazan 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*).

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Data

Animal Data

Vonoprazan:

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 unmated female rats from separate studies) during the period of organogenesis from gestation Day 6 to 17. During maternal dosing, one high-dose female died, and decreased body weight and food consumption occurred at the middle and highest doses. No embryo-fetal lethality was observed but decreased fetal body weight was observed in the highest dose group. Fetal abnormalities were limited to the 300 mg/kg/day dose group 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 embryofetal 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) during the period of organogenesis from gestation Day 6 to 18. Two animals aborted at the highest dose and decreased body weight and food consumption occurred at the mid and high doses. No embryo-fetal mortality or toxicity occurred. There were no external, visceral or skeletal abnormalities.

In a PPND study, pregnant female rats were orally administered vonoprazan at doses of 1, 3, 10, or 100 mg/kg/day (0.01, 0.18, 1.1, 22 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 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, a woman should pump and discard human milk for the duration of VOQUEZNA TRIPLE PAK or VOQUEZNA DUAL PAK therapy, and for 2 days after therapy ends, and feed her infant stored human milk (collected prior to therapy) or formula.

Data

Animal Data

Vonoprazan:

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 a comparison of AUC), 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 limited, non-standard, 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 an AUC values extrapolated from the PPND study) and on LD 14 at doses from 10 to 100 mg/kg/day (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.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate or well-controlled long-term studies have been performed to evaluate the effect of VOQUEZNA TRIPLE PAK and VOQUEZNA DUAL PAK on carcinogenesis, mutagenesis, or impairment of fertility.

Vonoprazan

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, gastropathy 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 adenoma 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 hepatocholangiocellular adenomas and 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 gastropathy 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 H₂-receptor antagonists.

Mutagenesis

Vonoprazan was negative for mutagenicity in the in vitro Ames test, in an in vitro clastogenicity assay in Chinese Hamster cells and in vivo in a rat bone marrow micronucleus study.

Impairment of Fertility

Vonoprazan at oral doses up to 300 mg/kg/day in rats (approximately 133 times the MRHD based on AUC from a separate study in nonpregnant animals administered the same dose) was found to have no effect on fertility and reproductive performance. Elongation of the estrous cycle was observed in rat at doses equivalent to 133 times the MRHD based on AUC.

17. PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise pregnant patients and females of reproductive potential that if pregnancy occurs while taking VOQUEZNA TRIPLE PAK, there is a potential risk to the fetus due to the clarithromycin component [*see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)*].

Advise patients who are exposed to VOQUEZNA TRIPLE PAK or VOQUEZNA DUAL PAK during pregnancy to contact Phathom Pharmaceuticals, Inc. at 1-800-775-PHAT (7428).

Lactation

Advise the lactating women to pump and discard their milk during treatment with VOQUEZNA TRIPLE PAK or VOQUEZNA DUAL PAK and for 2 days after the therapy ends [*see Use in Specific Populations (8.2)*].

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/s/

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 31, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 215151
Product Name and Strength:	Voquezna (vonoprazan) tablets, 10 mg and 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Phathom Pharmaceuticals, Inc
FDA Received Date:	March 17, 2022 and May 25, 2022
OSE RCM #:	2022-555
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Voquezna (vonoprazan) tablets, the Division of Gastroenterology (DG) requested that we review the proposed Voquezna prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1a Regulatory History

Voquezna Triple Pak (vonoprazan, amoxicillin, and clarithromycin) and Voquezna Dual Pak (vonoprazan and amoxicillin) were approved under a single prescribing information (PI) on May 3, 2022, for the treatment of H. pylori infection under NDA 215152 and NDA 215153, respectively. Voquezna tablets are proposed under a separate PI under NDA 215151. On May 25, 2022, Phathom added the approved indication and dosage regimen for H.pylori infection to the proposed PI per DG's request.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Phathom Pharmaceuticals, Inc.

4 RECOMMEDATIONS FOR DIVISION OF GASTROENTEROLOGY (DG)

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	(b) (4)	If important dose referencing information is presented under Table 1, it may be overlooked by the reader which could result in wrong dose errors.	Remove the footnoted sentence from under Table 1 and present it as a bullet under the Table 1.
2.	Three footnotes under Table 1, (b) (4) (b) (4)	(b) (4)	Consider removing the footnotes or present them as bullets under the table, if needed.
3.	Use of confusing symbol and abbreviation such as "<" or "GFR" found in Section 2.2	The usage of symbols and abbreviations can cause misinterpretation and confusion. ^a	Replace the symbol and abbreviation with their intended meaning.
4.	Section 2.2 (Dosage (b) (4) in Patients with Renal Impairment	Decreased readability of dosage adjustment information in special	To enhance accessibility of the dosage (b) (4)

^a ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) is text heavy and burdensome to read.	population may lead to dosing errors.	information, consider using bullets or a table format.

5 RECOMMENDATIONS FOR PHATHOM PHARMACEUTICALS, INC

Table 3. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The established name does not appear to be at least ½ the size of the proprietary name.	The size of the established name does not appear to comply with 21 CFR 201.10(g)(2).	Ensure the established name is at least ½ the size of the proprietary name as required per 21 CFR 201.10(g)(2).
2.	(b) (4)	The use of the same color font for different strengths and overlapping of color scheme of the proprietary name with one of the product strength minimize the difference between the strengths, which may lead to wrong strength selection errors.	Revise the color scheme (b) (4) so that either the strength or the proprietary name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.
3.	The dosage form statement (TABLETS) is overtly prominent.	Proprietary name and established name should be the most prominent information on the label in order to be in accordance with 21 CFR 201.10(g)(2).	Decrease the prominence of the dosage form statement by decreasing the font size, removing the bolded font, and removing the color.
4.	The net quantity statement is overly prominent and takes the reader's attention away from more important	Post-marketing experience shows that the risk of numerical confusion between the strength and net quantity increases	Decrease the prominence of net quantity statement by decreasing the font size and remove the bolding.

Table 3. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	product information, such as the product strength.	when the net quantity statement is more prominent.	
5.	The "Rx only statement" is overly prominent.	The increased prominence of the "Rx only statement" takes the reader's attention away from other important information on the PDP such as established name, dosage form, and strength	Decrease the prominence of the "Rx only statement" by decreasing the font size and removing the bolding.
6.	The usual dosage statement terminology is inconsistent with that used in the Prescribing Information.	21 CFR 201.55	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See Prescribing Information."
7.	As currently displayed, the manufacturer name("Phathom Pharmaceuticals") is more prominent in size than the most important information (i.e., proprietary name, established names strength, and dosage form). Additionally, the manufacturer name is duplicated on the side panel.	This takes readers' attention away from other important information such as proprietary name, established name(s), strength, and dosage form.	Decrease prominence of the manufacturer name and delete the duplicated manufacturer name.
Trade Container Label(s)			
1.	The format for expiration date is incorrect.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and

Table 3. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Sample Carton Labeling			
1.	The net quantity statement is duplicated on the Principal display panel (PDP).	The PDP should be reserved for important product information. Duplicative net quantity statement located on the PDP takes readers' attention away from more important information such as proprietary and established names, strength, and dosage form.	Remove the duplicative net quantity statement (5 TABLETS) at the bottom of the PDP as it is already presented on the top of the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Voquezna that Phathom Pharmaceuticals, Inc submitted on March 17, 2022.

Table 4. Relevant Product Information for Voquezna		
Initial Approval Date	N/A	
Active Ingredient	Vonoprazan	
Indication	Voquezna is indicated for the following indications: Healing of all grades of erosive esophagitis (EE) and relief of heartburn Maintenance of healing of all grades of EE and relief of heartburn	
Route of Administration	Oral	
Dosage Form	Tablets	
Strength	10 mg and 20 mg	
Dose and Frequency	Healing of EE and Relief of Heartburn	20 mg once daily
	Maintenance of Healed EE and Relief of Heartburn	10 mg once daily
How Supplied	Bottles of 30s	
Storage	Store between 20°C and 25°C (68°F and 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted [see USP Controlled Room Temperature].	

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Voquezna labels and labeling submitted by Phathom Pharmaceuticals, Inc.

- Container Labels received on March 17, 2022
- Sample Container Label received on March 17, 2022
- Sample Carton Labeling received on March 17, 2022
- Prescribing Information (Image not shown) received on May 25, 2022, available from <\\CDSESUB1\evsprod\nda215151\0008\m1\us\114-labeling\draft\labeling\voquezna-draft-labeling-text-25-may-2022-word.docx>

F.2 Label and Labeling Images



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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