CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215152Orig1s000
215153Orig1s000

OTHER REVIEW(S)

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:	May 2, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215152 and NDA 215153
Product Name and Strength:	Voquezna Triple Pak (vonoprazan; amoxicillin; clarithromycin) vonoprazan tablets, 20 mg; amoxicillin capsules, 500 mg; and clarithromycin tablets, 500 mg Voquezna Dual Pak (vonoprazan; amoxicillin) vonoprazan tablets, 20 mg and amoxicillin capsules, 500 mg
Applicant/Sponsor Name:	Phathom Pharmaceuticals, Inc.
OSE RCM #:	2021-1750-3 and 2021-1572-3
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 29, 2022 for Voquezna Triple Pak and Voquezna Dual Pak. The Division of Anti-Infectives (DAI) requested that we review the revised container labels and carton labeling for Voquezna Triple Pak and Voquezna Dual Pak (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]

[a] Birkemeier D. Label and Labeling Review for vonoprazan, amoxicillin, and clarithromycin Triple Pak and vonoprazan and amoxicillin Dual Pak (NDA 215152 and NDA 215153). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 APR 22. RCM No.: 2021-1750-2 and 2021-1752-2.

2 CONCLUSION

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

Appears this way on original

8 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

DAMON A BIRKEMEIER
05/02/2022 02:45:16 PM

MISHALE P MISTRY
05/03/2022 04:18:08 PM

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

Date:	April 27, 2022
Reviewer:	Hannah Day, PhD Division of Epidemiology II
Acting Team Leader:	Natasha Pratt, PhD Division of Epidemiology II
Deputy Division Director:	Monique, Falconer, MD, MS Division of Epidemiology II
OPE Deputy Director:	Michael Blum, MD, MPH
FDA Sentinel Program Lead:	Sarah Dutcher, PhD (designee)
OSE Deputy Director:	Robert Ball, MD, MPH, ScM
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	vonoprazan/amoxicillin/clarithromycin//vonoprazan/amoxicillin
Application Type/Number:	NDAs 215152/215153
Sponsor:	Phathom Pharmaceuticals Inc.
OSE RCM #:	2021-1751 and 2021-1749

1. BACKGROUND INFORMATION

1.1. Medical Product

Two New Drug Applications (NDA) were submitted in September 2021 for vonoprazan co-packaged with antibiotics for the treatment of *H. pylori* infection (VOQUEZNA TRIPLE PAK [NDA 215152 Vonoprazan/Amoxicillin/Clarithromycin] and VOQUEZNA DUAL PAK [NDA 215153 Vonoprazan/Amoxicillin]). Vonoprazan is new molecular entity which the applicant describes as a potassium-competitive acid blocker, a new class of acid-inhibitory agent. Vonoprazan was first approved as a stand-alone treatment for *H. pylori*, peptic and duodenal ulcers and esophagitis in Japan in 2014. In 2016, Japan authorized vonoprazan in combination with antibiotics for *H. pylori.* Vonoprazan is also authorized in several countries in Asia and Latin America. The two vonoprazan/antibiotic combinations in NDA 215152 and NDA 215153 were granted a Qualified Infectious Disease Product (QIDP) designation on May 5, 2021.

1.2. Describe the Safety Concern

According to the DPMH review, [1] animal data do not suggest safety concerns for pregnancy from the vonoprazan component of the VOQUEZNA TRIPLE PAK or VOQUEZNA DUAL PAK at relevant human doses. There were limited human data on pregnancy outcomes after vonoprazan exposure. Five cases of pregnancy were reported in the clinical trials. One of the five pregnant patients declined consent to pregnancy outcome information. The other four pregnancies resulted in two normal births, one spontaneous abortion and one elective abortion. The sponsor's pharmacovigilance database with information from approvals outside the United States was limited by a high percentage of unknown pregnancy outcomes (51/108). [1] In the other 57 live births with known outcomes reported, there were no major or minor congenital malformations. [1] The proposed product label carries embryo-fetal toxicity warnings (in Section 5.2, 8.1, 17) only for VOQUEZNA TRIPLE PAK due to the clarithromycin component. [2]

A recent meta-analysis estimated a pooled *H. pylori* prevalence of 35.6% in the United States. [3] So there is the potential for wide use of this product. The Division of Pediatric and Maternal Health (DPMH) recommended a post-marketing requirement (PMR) for a pregnancy exposure registry and a pregnancy study of a different design to assess the safety of using these vonoprazan-containing products during pregnancy.[1]

The Division of Epidemiology-II was consulted by the Division of Anti-infectives to evaluate if Sentinel ARIA can be used to conduct this PMR study.

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). †

† ***If checked, please complete General ARIA Sufficiency Template.***

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

☒ Outcomes

☒ Covariates

☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes ARIA lacks access to medical records. The pregnancy registry being considered requires medical chart review of congenital malformations by physicians with expertise in birth defects.

Covariates ARIA does not have detailed information on potential confounders. Specifically, *H. pylori* is associated with lower socioeconomic status (SES)[4] which is associated with outcomes such as major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth. The pregnancy registry being considered would collect detailed narratives with information on covariates.

Analytical Tools ARIA data mining methods have not been fully tested and implemented for maternal and fetal outcomes.

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

The proposed language as of the February 22, 2022 late cycle meeting is as follows:

- Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Triple Pak and/or Dual Pak 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.
- 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 Triple Pak and/or Dual Pak during pregnancy compared to an unexposed control population.

3. References

1. Liedtka, J. Pregnancy and Lactation Labeling for [redacted] TRIPLE PAK (Vonoprazan/Amoxicillin/Clarithromycin) and [redacted] DUAL PAK (Vonoprazan/Amoxicillin), NDA 215152 and NDA215153. March 24, 2022. 2. [redacted] TRIPLE PAK and [redacted] DUAL PAK Draft Label as of March 29, 2022, accessed March 29, 2022

2. [redacted] TRIPLE PAK and [redacted] DUAL PAK Draft Label as of March 29, 2022, accessed March 29, 2022

3. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology. 2017 Aug;153(2):420-429. doi: 10.1053/j.gastro.2017.04.022. Epub 2017 Apr 27. PMID: 28456631.

4. Tsang SH, Avilés-Santa ML, Abnet CC, Brito MO, Daviglus ML, Wassertheil-Smoller S, Castañeda SF, Minnerath S, Talavera GA, Graubard BI, Thyagarajan B, Camargo MC. Seroprevalence and Determinants of Helicobacter pylori Infection in the Hispanic Community Health Study/Study of Latinos. Clin Gastroenterol Hepatol. 2022 Mar;20(3):e438-e451. doi: 10.1016/j.cgh.2021.02.042. Epub 2021 Mar 2. PMID: 33667677; PMCID: PMC8410907.

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/

HANNAH R DAY
04/27/2022 11:41:45 AM

CHIH-YING CHEN
04/27/2022 11:43:48 AM

MONIQUE FALCONER
04/27/2022 11:50:27 AM

MICHAEL D BLUM
04/27/2022 12:40:39 PM

SARAH K DUTCHER
04/27/2022 02:08:30 PM

ROBERT BALL
04/27/2022 03:05:17 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:	April 22, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215152 and NDA 215153
Product Name and Strength:	vonoprazan; amoxicillin; clarithromycin vonoprazan tablets, 20 mg; amoxicillin capsules, 500 mg; and clarithromycin tablets, 500 mg vonoprazan; amoxicillin vonoprazan tablets, 20 mg and amoxicillin capsules, 500 mg
Applicant/Sponsor Name:	Phathom Pharmaceuticals, Inc.
OSE RCM #:	2021-1750-2 and 2021-1752-2
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 29, 2022 for vonoprazan; amoxicillin; and clarithromycin Triple Pak and for vonoprazan; amoxicillin Dual Pak. The Division of Anti-Infectives (DAI) requested that we review the revised container labels and carton labeling for vonoprazan; amoxicillin; and clarithromycin Triple Pak and for vonoprazan; amoxicillin Dual Pak (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

We note that the carton and container labels were updated to change the proposed proprietary names to Voquezna Dual Pak*** and Voquezna Triple Pak***, respectively. However, the acceptability of the proposed proprietary names is still under review under separate cover.

Additionally, we note that based on testing in older adults, Phathom revised the directions for opening the blister on the sample and retail blister cards. Furthermore, Phathom corrected the barcodes on the retail cartons to reflect the correct NDCs.

As proposed, the container label for the Dual Pak can be improved from a medication error perspective and we have the following recommendations:

- For the Dual Pak, step 1 on the back side currently states, "Cut off the AM doses along the dashed scissors line on the back of the card." We note that the dashed scissors line is located along the bottom of the tablet/capsule rows for each AM, MID-DAY, and PM dose, and as currently depicted the location of the dashed scissors line may lead users to try and secure an opening using the back side of the package which would be incongruent with step 2, "Looking at the Front of the AM doses, carefully cut…". Additionally, we are concerned that based on the location of the scissors line, there is an increased risk of end users inadvertently cutting through the capsules or tablets if attempting to secure an opening using the back of the blister pack as a guide. In order to successfully "cut off" the AM doses as instructed in step 1 (and subsequently "cut off" the MID-DAY and PM doses in steps 4 and 5), it appears the dashed scissors line would need to appear above the words "AM", "MID-DAY", and "PM". We recommend revising the container label of the Dual Pak to relocate the dashed scissors line above the doses instead of below the doses.
- For the Dual Pak, we note slight variation in the wording used for steps 4 and 5 on the back side of the pak; "In the afternoon, repeat the steps above…" *versus* "(b) (4) We believe the phrase "repeat the steps above" provides better clarity for the end user. We recommend revising step 5 to state "In the evening, repeat steps 1-3 above…".

9 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

DAMON A BIRKEMEIER
04/22/2022 10:35:24 AM

VALERIE S VAUGHAN
04/22/2022 10:49:30 AM

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

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

Memorandum

Date: 4/6/2022

To: Eva Zuffova
Regulatory Project Manager
Division of Regulatory Operations for Infectious Disease

From: Nima Ossareh, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for (b) (4) TRIPLE PAK and (b) (4) DUAL PAK

NDA: 215152, 215153

In response to DAI consult request dated September 16, 2021, OPDP has reviewed the proposed product labeling (PI) for (b) (4) TRIPLE PAK and (b) (4) DUAL PAK.

PI: OPDP does not have any comments on the proposed labeling at this time.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

41 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

NIMA OSSAREH
04/06/2022 02:40:21 PM

Clinical Inspection Summary

Date	5 April 2022
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Eva Zuffova, Ph.D., RPM Mayurika Ghosh, M.D., Medical Reviewer Thomas Smith, M.D., Medical Team Leader Dmitri Iarikov, M.D., Ph.D. Division Director Division of Anti-Infectives (DAI)
NDA #	215152 and 215153
Applicant	Phathom Pharmaceuticals, Inc.
Drug	(b) (4) Triple Pak (vonoprazan tablets 20mg, amoxicillin capsules 500 mg and clarithromycin tablets 500 mg)
NME	Yes
Proposed Indication	Treatment of *Helicobacter pylori* infection
Consultation Request Date	25 Oct 2021
Summary Goal Date	6 Apr 2022
Action Goal Date	3 May 2022
PDUFA Date	3 May 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Ciesiolkiewicz-Wojcik, Jamrozik-Kruk, and Lopez were inspected in support of NDAs 215152 and 215153, covering one clinical trial, HP-301.

During the clinical investigator inspections, the source records (i.e., 13C-urea breath test [13C-UBT] results) related to the primary efficacy endpoint (i.e., *Helicobacter pylori [H. pylori]* eradication at Week 6) were reviewed and verified against the sponsor's data line listings for all the 185 randomized subjects at these 3 sites. No discrepancies were noted.

The source records that were necessary to verify the modified Intent-to-Treat primary (MITTp) analysis population (i.e., *H. pylori* identification by histology and by culture and *H. pylori* susceptibility test results) were also verified against the sponsor's data line listings. *H. pylori* histology test results were verified during the clinical investigator inspections for all 185 randomized subjects at the 3 sites. No discrepancies were noted.

However, reporting errors by the central laboratory (i.e., (b) (4) at 2 of the 3 sites were noted that included incorrectly indicating the presence of *H. pylori* (e.g., false positives) or the presence of dysplasia or adenocarcinoma. In a 10 March 2022 response to an Information

Request (IR), the sponsor explained that beginning in February 2020, they identified reporting errors that required changes to the reported histology results for 34 subjects at approximately 17 sites. Incorrect reporting of the presence of *H. pylori* occurred in 23 subjects (i.e., false positives in 22 subjects and false negative in one subject); incorrect reporting of dysplasia occurred in 8 subjects; and incorrect reporting of adenocarcinoma occurred in 2 subjects. The sponsor noted that the causes of the errors were due to the following:

- A pathologist over-calling the presence of *H. pylori* by judging sporadic, low-level positive background staining to indicate the presence of *H. pylori*
- Poor database design issues that contributed to incorrect selection of the diagnosis (e.g., dysplasia, adenocarcinoma) from drop-down boxes in the result entry interface of the (b) (4) database
- Inadequate review of the histology results prior to the pathologist digitally signing the report

The errors were corrected prior to database lock and study unblinding, which occurred on 19 Apr 2021. The sponsor also noted that re-evaluation of the histology samples involved a consensus review by at least two pathologists. The sponsor's corrective and preventative action plan implemented appear to be sufficient and the histology result reporting error issue should have no impact on the overall efficacy results of the study.

In addition, *H. pylori* identification by culture and susceptibility test results that were necessary to verify the MITTp analysis population could not be verified during the inspection for any of the randomized subjects because the source records (i.e., first original recording or certified copies of the first original recording of the data) documenting these test results were not available at the sites. In a 26 Jan 2022 response to an IR, the sponsor submitted certified copies of the *H. pylori* culture and susceptibility reports from the central laboratory (i.e., (b) (4) to the NDA for all randomized subjects (n=1046). Certified copies of these reports were reviewed and verified by this reviewer against the sponsor's data listings for the 137 of 185 randomized subjects at the 3 sites inspected (i.e., 13% of the total randomized study population). No issues or discrepancies were noted.

Overall, 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

NDAs 215152 and 215153 were submitted in support of the use of vonoprazan (a potassium-competitive acid blocker) for the treatment of adults, (b) (4), with *H. pylori* infection. A pivotal study supporting the application was the following:

- Protocol HP-301, "Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy with Oral Vonoprazan 20 mg or Double-Blind Triple Therapy with Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy with Oral Lansoprazole 30 mg Daily in Patients with *Helicobacter Pylori* Infection."

Protocol HP-301 was a randomized, parallel-group study to compare the efficacy and safety of vonoprazan open-label dual therapy (vonoprazan and amoxicillin) and vonoprazan double-blind triple therapy (vonoprazan, amoxicillin, and clarithromycin) administered for 14 days compared to lansoprazole double-blind triple therapy (lansoprazole, amoxicillin, and clarithromycin) administered for 14 days in *H. pylori*-positive subjects. The primary objective was to compare the efficacy of *H. pylori* eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in *H. pylori*-positive subjects who did not have a clarithromycin- or amoxicillin-resistant strain of *H. pylori* at baseline.

- ***Subjects:*** A total of 3385 subjects were screened and 1046 were randomized (i.e., 349 subjects were randomized to vonoprazan dual therapy, 349 to vonoprazan triple therapy, and 348 to lansoprazole triple therapy

- ***Sites:*** The study was conducted at 103 sites: 71 in the US and 32 in Europe

- ***Study initiation and completion dates:*** 10 Dec 2019 (first subject signed informed consent); 10 March 2021 (last subject's last visit for the primary endpoint); and 18 March 2021 (last subject's last visit/contact)

- ***Database Lock Date:*** 19 April 2021

- ***Study Unblinding:*** 19 April 2021

The study consisted of the following:

- Screening Period (Day -35 to Day -2; Visit 1)
- Treatment Period (2-week Treatment Period; Visit 2 and Visit 3)
- Follow-up Period (Week 4 phone call and Visit 4, four weeks after the last dose of study drug)

During the screening period, subjects provided informed consent and underwent screening assessments to determine study eligibility, and baseline assessments were performed.

A 13C-UBT was performed during the Screening Period to establish *H. pylori* infection status. Prior to the performance of the 13C-UBT, subjects were not to have received any medications that could have interfered with the test. Subsequently, an endoscopy was performed to collect gastric mucosal biopsy specimens at the start of the study for histopathology to document *H. pylori* infection. Two additional gastric mucosal biopsy specimens were collected for culture and susceptibility testing of the bacteria to clarithromycin, amoxicillin, and metronidazole antibiotics, which are commonly used in the treatment of *H. pylori* infection.

Results from the gastric mucosal biopsy specimens (i.e., histology, culture, and susceptibility results) were not necessary to confirm eligibility and were reported after randomization.

During the treatment period, *H. pylori*-positive subjects whose eligibility was confirmed by 13C-UBT during the Screening Period were randomly assigned via an interactive response

technology (IRT) system in a 1:1:1 ratio to one of the following treatment arms:

- Vonoprazan dual therapy arm: Open-label vonoprazan 20 mg twice daily (BID) in conjunction with amoxicillin 1000 mg TID for 14 days
- Vonoprazan triple therapy arm: Blinded vonoprazan 20 mg BID in conjunction with amoxicillin 1000 mg BID and clarithromycin 500 mg BID for 14 days
- Lansoprazole triple therapy arm/control arm: Blinded lansoprazole 30 mg BID in conjunction with amoxicillin 1000 mg BID and clarithromycin 500 mg BID for 14 days

A double-blind design was employed for the triple therapy groups so that both the Investigators, the subjects, (b) (4) personnel, and the Phathom Pharmaceuticals, Inc. team including the study statistician were blinded to the treatment assignments.

The dual therapy group was open-label; therefore, the site, subjects, some (b) (4) personnel, and the Phathom Pharmaceuticals, Inc. team were unblinded to the dual therapy regimen. Although the dual therapy regimen was open-label, the primary endpoint for this study was based on an objective measurement, the 13C-UBT, and the UBT testing facility should have remained blinded to all 3 treatment assignments, ensuring that the evaluation of the efficacy endpoint was not subject to bias. Subjects returned at Week 2 for safety assessments, return of study drug, and review of treatment compliance.

During the Follow-up Period, a phone call was performed at Week 4 (2 weeks after last dose of study drug) to assess concomitant medication usage and any AEs. At Week 6 (4 weeks after the last dose of study drug), *H. pylori* eradication status was assessed by 13C-UBT. Subjects who remained *H. pylori*-positive at this visit were to have a follow-up endoscopy with repeat biopsies for culture and susceptibility testing to inform the investigators about appropriate treatment per standard of clinical care.

A subject was considered to have completed the study if he/she had completed all study periods, including Visit 4, which was performed 4 weeks after the last dose of study drug.

The ***primary efficacy endpoint*** was the proportion of subjects with successful *H. pylori* eradication after the Treatment Period, as determined by 13C-UBT, at 4 weeks after the last dose of study drug (Week 6, Visit 4), in subjects who did not have a clarithromycin- or amoxicillin-resistant strain of H. pylori at baseline (Screening, Visit 1).

The following central laboratories were contracted to perform trial-related activities related to the primary efficacy endpoint data:

- (b) (4) was a central laboratory used to process and analyze the 13C-UBTs and manage the resultant data.
- (b) (4) was the central laboratory used to perform *H. pylori* culture and susceptibility testing and manage the resultant data.
- (b) (4) was the central laboratory used to perform *H. pylori* histology testing and manage the resultant data.

Of note, the MITTp set was used for the primary analysis. The MITTp set was a subset of subjects in the MITT set who did not have a clarithromycin or amoxicillin resistant strain of *H. pylori* at baseline. Of note, the MITT Set included all subjects randomized into the study who had *H. pylori* infection documented by 13C-UBT and biopsy by culture or histology at baseline.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, high incidence of important and non-important protocol deviations, site-specific efficacy results, and prior inspectional history.

III. RESULTS (by site):

1. **Agnieszka Ciesiolkiewicz-Wojcik, MD**
   Site# 48011
   ul. Marii Curie- Sklodowskiej 12
   Wroclaw, Dolnoslaskie 50-381
   Poland
   PDUFA Inspection Dates: 17 to 21 Jan 2022

At this site, per the sponsor's data line listings, 198 subjects were screened, 71 were randomized, and 69 subjects completed the study. Subject (b) (6) (randomized to vonoprazan triple therapy) withdrew from the study due to adverse events of mouth bleeding and elevated liver function tests, and Subject (b) (6) (randomized to vonoprazan dual therapy) withdrew due to a new diagnosis of a lung tumor.

A full audit of the study records for the 71 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 efficacy endpoint of *H. pylori* eradication as well as inclusion in the MITTp (the primary analysis population); adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

There was one unreported adverse event of worsening hypocalcemia in Subject (b) (6) (randomized to vonoprazan dual therapy) during the 2-week Treatment Period (Visit 3, Day 15). The subject's calcium level was (b) (6) mg/dL at screening ((b) (6)), and at that time the investigator had prescribed calcium carbonate 500 mg once daily. On (b) (6), safety laboratories showed that the subject's calcium level had dropped to (b) (6) mg/dL, and the calcium carbonate dose was increased to 500 mg three times per day.

Reviewer's comment: *The missing adverse event data of worsening hypocalcemia in Subject (b) (6) is an isolated incident and is unlikely to impact the overall safety results of the study. This issue was discussed with Dr. Ciesiolkiewicz-Wojcik during the inspection close-out meeting. Dr. Ciesiolkiewicz-Wojcik acknowledged the under-reporting and promised improvements in the future.*

The source records documenting *H. pylori* identification at Screening and eradication at Week 6 (i.e., *H. pylori* histology test results performed by the central laboratory, (b) (4) and 13C-UBT results performed by the central laboratory, (b) (4) were reviewed and verified against the sponsor's data line listings for the 71 randomized subjects. No discrepancies were noted.

Of note, *H. pylori* culture and susceptibility test results performed by the central laboratory, (b) (4) that were necessary to verify the MITTp population, could not be verified during the inspection for any of the randomized subjects because the source records (i.e., first original recording or certified copies of the first original recording of the data) documenting these test results were not available at the site.

Reviewer's comment*: In a 26 Jan 2022 response to an IR, the sponsor submitted certified copies of the H. pylori culture and susceptibility reports from the central laboratory ((b) (4) to the NDA. Certified copies of these reports were reviewed and verified by this reviewer against the sponsor's data listings for the 50 of the 71 randomized subjects. No issues or discrepancies were noted.*

Initial reporting errors in the identification of *H. pylori* by histology testing were noted to have occurred in 3 subjects (Subjects (b) (6) incorrectly indicating the presence of *H. pylori* (i.e., false positives). The central laboratory re-evaluated the histology samples and corrected the reporting errors.

Reviewer's comment: *To better understand the scope and extent of these histology reporting errors, an IR was sent to the sponsor after the inspection. In a 10 March 2022 response to the IR, the sponsor explained that beginning in February 2020, they identified reporting errors that required changes to the reported histology results for 34 subjects at approximately 17 sites.*

Incorrect reporting of the presence of H. pylori occurred in 23 subjects (i.e., false positive in 22 subjects and false negative in one subject); incorrect reporting of dysplasia occurred in 8 subjects; and incorrect reporting of adenocarcinoma occurred in 2 subjects. In the 10 March 2022 response to the IR, the sponsor noted that the causes of the errors were due to the following:

- *A pathologist over-calling the presence of H. pylori by judging sporadic, low-level positive background staining to indicate the presence of H. pylori*
- *Poor database design issue that contributed to incorrect selection of the diagnosis (e.g., dysplasia, adenocarcinoma) from drop-down boxes in the result entry interface of the (b) (4) database*

- *Inadequate review of the histology results prior to the pathologist digitally signing the report*

All errors were identified and corrected by 22 Feb 2021, prior to database lock and study unblinding, which occurred on 19 Apr 2021. The sponsor also stated that re-evaluation of the histology samples involved a consensus review by at least two pathologists. The sponsor's corrective and preventative action plan that was implemented appears to be sufficient, and the reporting error issue should have no impact on the overall efficacy results of the study.

2. Zofia Jamrozik-Kruk, MD
Site# 48017
Waly Dwernickiego 43/45
Czestochowa, 42-202
Poland
PDUFA Inspection Dates: 31 Jan to 2 Feb 2022

At this site, 131 subjects were screened, 46 were randomized, and 41 subjects completed the study. Four subjects withdrew from the study due to adverse events: increased abdominal pain in Subject [redacted] (randomized to lansoprazole triple therapy), diarrhea and dizziness in Subject [redacted] (randomized to lansoprazole triple therapy), burning tongue in Subject [redacted] (randomized to vonoprazan triple therapy), and hypertension in Subject [redacted] (randomized to vonoprazan triple therapy). Subject [redacted] withdrew prior to starting the investigational product (randomized to vonoprazan triple therapy).

A full audit of the study records for the 46 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 efficacy endpoint of *H. pylori* eradication as well as inclusion in the MITTp (the primary analysis population); adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

There was no evidence of under-reporting of adverse events. The source records documenting *H. pylori* identification at Screening and eradication at Week 6 (i.e., *H. pylori* histology test results performed by the central laboratory, [redacted] and 13C-UBT results performed by the central laboratory, [redacted] were reviewed and verified against the sponsor's data line listings for the 46 randomized subjects. No discrepancies were noted.

Of note, *H. pylori* culture and susceptibility test results performed by the central laboratory, [redacted] that were necessary to verify the MITTp population could not be verified during the inspection for any of the randomized subjects because the source records (i.e., first original recording or certified copies of the first original recording of the data) documenting these test results were not available at the site.

Reviewer's comment*: In a 26 Jan 2022 response to an IR, the sponsor submitted certified copies of the H. pylori culture and susceptibility reports from the central laboratory (* (b) (4) *to the NDA. Certified copies of these reports were reviewed and verified by this reviewer against the sponsor's data listings for the 46 randomized subjects. No issues or discrepancies were noted.*

Reporting errors in the identification of *H. pylori* by histology were also noted to have occurred in 1 subject at this site (Subjects (b) (6)), incorrectly indicating the presence of *H. pylori* (i.e., false positive). The central laboratory re-evaluated the histology sample and corrected the reporting error before the database lock.

3. Luis Lopez, MD
Site# 10122
8011 N Himes Ave Ste 2
Tampa, FL 33614
PDUFA Inspection Dates: 24 to 28 January 2022

At this site, 110 subjects were screened, 68 were randomized, and 67 subjects completed the study. One subject (Subject (b) (6)) withdrew from the study due to adverse events of mild abdominal pain, nausea, loose stools, and anorexia.

A full audit of the study records for the 68 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 efficacy endpoint of *H. pylori* eradication as well as inclusion in the MITTp (the primary analysis population); adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

There was no evidence of under-reporting of adverse events. The source records documenting *H. pylori* identification at Screening and eradication at Week 6 (i.e., *H. pylori* histology test results performed by the central laboratory, (b) (4) and 13C-UBT results performed by the central laboratory, (b) (4) were reviewed and verified against the sponsor's data line listings for the 68 randomized subjects. No discrepancies were noted.

Of note, *H. pylori* culture and susceptibility test results performed by the central laboratory, (b) (4) that were necessary to verify the MITTp population could not be verified during the inspection for any of the randomized subjects because the source records (i.e., first original recording or certified copies of the first original recording of the data) documenting these test results were not available at the site.

Reviewer's comment*: In a 26 Jan 2022 response to an IR, the sponsor submitted certified copies of the H. pylori culture and susceptibility reports from the central laboratory (* (b) (4) *to*

the NDA. Certified copies of these reports were reviewed and verified by this reviewer against the sponsor's data listings for the 41 of the 68 randomized subjects. No issues or discrepancies were noted.

{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.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Division Director
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. NDAs 215152 and 215153
DAI/Project Manager/Eva Zuffova
DAI/Medical Reviewer/Mayurika Ghosh
DAI/Medical Team Leader/Thomas Smith
DAI/Division Director/Dmitri Iarikov
OSI/DCCE/Branch Chief/Kassa Ayalew
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
04/05/2022 09:47:45 AM

PHILLIP D KRONSTEIN
04/05/2022 09:54:11 AM

KASSA AYALEW
04/05/2022 10:14:07 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: 3/24/22 **Date Consulted:** 12/20/21

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

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

Lynne P. Yao, MD, Director, DPMH

To: Eva Zuffova, Regulatory Project Manager (RPM)
Division of Anti-infectives (DAI)

Drug/NDA: (b) (4) Triple Pack (Vonoprazan/Amoxicillin/Clarithromycin), N 215152
(b) (4) Dual Pak (Vonoprazan/Amoxicillin), N 215153

Indication: Treatment of *Heliobacter pylori* (*H. pylori*) infection

Applicant: Phathom Pharmaceuticals

Subject: Pregnancy and Lactation Labeling [505b (2) New Drug Application (NDA)]

Materials Reviewed:

- Applicant's submission dated 9/3/21
- DPMH review for Moxatag (amoxicillin), NDA 50813. Jeanine Best, MSN, RN, PNP 9/17/19. DARRTS Reference ID # 4492936[1,2].

[1]DPMH review for Moxatag (amoxicillin), NDA 50813. Jeanine Best, MSN, RN, PNP 9/17/19. DARRTS Reference ID # 4492936

[2] The Moxatag and Biaxin reviews were part of the materials reviewed but were not a source relied upon for the labeling recommendations below. Although there is overlap in the labeling proposed for (b) (4) Triple Pack (Vonoprazan/Amoxicillin/Clarithromycin), N 215152 and (b) (4) Dual Pak (Vonoprazan/Amoxicillin), N 215153 and that being proposed here, the labeling recommendations in this review are based on DPMH's independent analysis of the underlying data.

- DPMH review for Biaxin (clarithromycin); NDA 50-662, 50-775, 50-698. Leyla Sahin, M.D. 3/18/13. DARRTS Reference ID # 3278259[2,3.]

Consult Question: Please review the proposed labeling language in section 8.1, 8.2, 8.3.

INTRODUCTION AND BACKGROUND

- On 9/3/21, Phathom Pharmaceuticals submitted two 505b (2) NDAs, 215152 (b) (4) Triple Pack (vonoprazan/amoxicillin/clarithromycin) and 215153 (b) (4) Dual Pack (vonoprazan/amoxicillin) to DAI for the treatment of *H. pylori* infection. Amoxil (N 50459) and Biaxin (N50662) as well as amoxicillin (ANDA 64076) and clarithromycin (ANDA 65136) are the listed drugs relied upon.
- On 12/20/21 DAI consulted DPMH to assist with the proposed labeling language for Section 8.
- Vonoprazan belongs to a new class of acid-inhibitory agents called potassium-competitive acid blockers (PCAB). Vonoprazan has 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 have been additional approvals in Asia and Latin America. According to the applicant, cumulatively over 50 million patients have been exposed to vonoprazan since 2014.
- The recommended adult oral dosage of (b) (4) TRIPLE PAK is vonoprazan 20 mg plus amoxicillin 1000 mg plus clarithromycin 500 mg, each given twice daily, for 14 days to be taken in the morning and evening with or without food.
- The recommended adult oral dose of (b) (4) DUAL PAK is vonoprazan 20 mg given twice daily in the morning and evening plus amoxicillin 1000 mg three times daily in the morning, mid-day, and evening, for 14 days with or without food.

Table 1: Drug Characteristics[4]

	Vonoprazan 20 mg	**Amoxicillin**	**Clarithromycin**
Half life	9.8 hours +/- 1.8	1.3 hours +/- 0.1	4.6 hours +/- 0.5 Metabolite=8.0 +/-
Molecular weight	461.4 Daltons	419.4	747.9
Protein-binding	85-88%	17%	72% but binding ↓ with increasing concentration

Source: Reviewer's Table

[3] DPMH review for Biaxin (clarithromycin); NDA 50-662, 50-775, 50-698. Leyla Sahin, M.D. 3/18/13. DARRTS Reference ID # 3278259

[4] Japanese labeling from 2020 provided by the applicant.

H. Pylori Infection (HPI) and Pregnancy

Symptomatic HPI during pregnancy is thought to be uncommon[5]. HPI is associated with the development of peptic ulcer disease. In 1953, before appropriate therapy was available, Clark reported that 90% of the 313 pregnant women with peptic ulcer disease studied had remission during pregnancy, however, with symptom recurrence by 3 months to 2 years postpartum.[6] More recent publications suggest an association with HPI and hyperemesis gravidarum; however, findings are inconsistent and the etiology of hyperemesis gravidarum which still remains unknown, seems to be multifactorial and may be the final result of various unrelated conditions.[7],[8] An association with HPI and systemic inflammation in preeclampsia has also been reported.[9] It is hypothesized that preexisting HPI and gastritis could predispose some pregnant women to severe nausea and vomiting, and subsequent adverse birth outcomes (i.e., low birthweight, prematurity, small for gestational age).[10]

Current thinking in the field is that eradication of HPI during pregnancy is not recommended, but the decision to treat would be based on the severity of hyperemesis gravidarum symptoms.[11] Suggested first line treatment regimens for pregnant women with HG disease severity requiring treatment include triple therapy with a proton pump inhibitor (PPI), clarithromycin and metronidazole or amoxicillin for 14 days.[1,5] Metronidazole would be used instead of amoxicillin for first line treatment in patients with penicillin allergy. First line bismuth quadruple regimens (PPI, metronidazole, tetracycline, bismuth) which may be used in the case of penicillin allergy and prior macrolide exposure, include bismuth and tetracycline, are not recommended in pregnancy due to the drugs' teratogenic potential. Treatment of HPI is often deferred until postpartum.[12]

In 2019, Nguyen[13] noted that "eradication of H. pylori led to symptom alleviation of hyperemesis gravidarum in case reports, case series and small research reports" and

---

[5]1 Cunningham F, Leveno KJ, et al., Gastrointestinal Disorders. In: Cunningham F, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS. eds. Williams Obstetrics, Twenty-Fourth Edition. New York, NY: McGraw-Hill; 2013. http://accessmedicine.mhmedical.com/content.aspx?bookid=1057&Sectionid=59789199. Accessed August 18, 2016.

[6] Clark DH. 1953. Peptic ulcer in women. British Medical Journal 1: 1254– 1257.

[7] Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstet Gynecol. 2007 Sep;110(3):695-703.

[8] Cardaropoli S et al. Helicobacter pylori and pregnancy-related disorders. World J Gastroenterol . 2014 Jan 21;20(3):654-64.

[9] UstUn Y, Engin-Ustin Y, et al. Association of helicobactor pylori with systemic inflammation in preeclampsia. J Mat Fet Neon Med. 2010 Apr, 23(4):311-4

[10] Grooten IJ, Den Hollander WJ, Roseboom TJ, Kuipers EJ, Jaddoe VW, Gaillard R, Painter RC. Helicobacter pylori infection: a predictor of vomiting severity in pregnancy and adverse birth outcome. Am J Obstet Gynecol. 2017 May;216(5): 512.e1-512.e9. doi: 10.1016/j.ajog.2017.01.042. Epub 2017 Feb 7.

[11] van der Woude CJ, Metselaar HJ, Danese S. Management of gastrointestinal and liver diseases during pregnancy. Gut 2014; 63:1014-1023.

[12] Speichinger E, Holschneider CH. Chapter 25. Surgical Disorders in Pregnancy. In: DeCherney AH, Nathan L, Laufer N, Roman AS. eds. CURRENT Diagnosis & Treatment: Obstetrics & Gynecology, 11e New York, NY: McGraw-Hill; 2013. http://accessmedicine.mhmedical.com/content.aspx?bookid=498&sectionid=41008616. Accessed December 10, 2017.

[13] Nguyen CT et al. Treatment of Helicobacter pylori in Special Patient Populations. Pharmacotherapy. 2019 Oct;39(10):1012-1022. doi: 10.1002/phar.2318. Epub 2019 Sep 2. PMID: 31400244.

described potential candidates for treatment during pregnancy in a publication entitled "Treatment of Helicobacter pylori in Special Patient Populations".

> For patients experiencing hyperemesis gravidarum, careful consideration of risks versus benefits of therapy should be discussed before proceeding with treatment… However, those undergoing treatment during the first trimester should substitute metronidazole for clarithromycin… Balancing risk of maternal and fetal harm and benefit of symptom resolution should be used to decide treatment duration. Initial conservative treatment with a short course of seven days may alleviate symptoms and minimize risks.[14,15]

Current State of the Labeling
Not applicable for vonoprazan since not yet approved in the US.
See Attachment A for "Current State of Labeling for Amoxicillin and Clarithromycin".

REVIEW

Pregnancy - Vonoprazan

Nonclinical Experience
In pregnant rats, no adverse effects were noted after oral administration of 100 mg/kg/day vonoprazan, approximately 27 times the MRHD based on AUC exposure comparisons. In a pre- and postnatal development study, pups of dams orally administered 100 mg/kg/day vonoprazan (approximately 22 times the MRHD based AUC data), during gestation and lactation, exhibited liver necrosis and hemorrhage. These effects were not observed at 10 mg/kg/day (approximately equal to the MRHD based on AUC data).

Review of Pharmacovigilance Database (PVDB)
The original submission on 9/3/21 for the (b) (4) Triple Pak NDA under "labeling history" included a small amount of data regarding the PVDB for vonoprazan. The 5 cases of pregnancy reported in the Phase 1 to 3 completed and ongoing studies at the time of the 2019 PLLR submission are provided below in Table 2.

Table 2: Pregnancy Cases Reported in Clinical Studies

Clinical Study	Case Description
TAK-438_109, Section 12.3.2 Narratives	Pregnancy was reported for 1 female subject (Subject ID: (b) (6) in the vonoprazan 20 mg group. The subject had **a spontaneous miscarriage** (early pregnancy loss) approximately one month after the subject received vonoprazan.
TAK-438/CCT-102, Section 12.5.3 Pregnancy	Pregnancy was reported for 1 female subject (Subject ID: (b) (6) in the vonoprazan 20 mg group. The subject had a **normal birth at 40 weeks** of pregnancy. No congenital abnormalities were observed.

[14] Ono Y et al. Effectiveness of Helicobacter pylori eradication in pregnant women with idiopathic thrombocytopenic purpura. J Obstet Gynaecol Res 2017; 43:1212–6.
[15]Strachan BK, Jokhi RP, Filshie GM. Persistent hyperemesis gravidarum and Helicobacter pylori. J Obstet Gynaecol 2000;20 (4):427.

TAK-438/OCT-301, Section 12.5.3 Pregnancy	Pregnancy was reported for 1 female subject (Subject ID: (b) (6) in the vonoprazan 20 mg group. The subject had a **normal birth on 39 weeks** and 5 days of her pregnancy, which was 242 days after completing study treatment.
TAK-438_304, Section 12.5.4 Pregnancy	One subject (Subject ID: (b) (6)) in the vonoprazan group had a positive pregnancy test at the study termination visit and underwent **elective abortion**.
EE-301	One pregnancy was reported for 1 female subject (Subject ID: (b) (6) (b) (6)) in the **ongoing** study which is blinded. The subject declined consent to pregnancy outcome information.

Source: Applicant's "Labeling History" submitted on 9/3/21, pg. 8/10.

In the 2019 submission for PLLR, the applicant provided a table with minimal data on 108 cases reported in the "Pregnancy, Puerperium and Perinatal Conditions" SOC from their PVDB in the postmarketing period. DPMH sent an information request asking the division to provide all known information about these cases. See Attachment A Table 6 and Table 7 for a summary of the data from the IR response.

Reviewer's Comment
Except for the clinical trial cases, there was a great deal of missing information on the pregnancies from the PVDB. Outcomes were available for 9 clinical trial pregnancies (4 live births, 2 TAB, 3 SAB) and 48 post-marketing pregnancies [57 live births (10 sets of twins), one abortion (not otherwise specified)]. This left 51/108 (47%) pregnancies with unknown outcomes. Overall, the results are reassuring in that none of the cases with known outcomes reported a major or minor congenital malformation.

Applicant's Review of Literature
The original submission on 9/3/21 for the (b) (4) Triple Pak NDA under "labeling history" included a review and summary of published information on the use of vonoprazan in pregnant individuals in the following databases: AdisInsight: Drugs, AdisInsight: Trials, BIOSIS Previews®, COVID-19 Research, Embase®, MEDLINE®, Morressier Life Science Conference Abstracts and Posters, Publicly Available Content. The only publication identified by the applicant described a nonclinical publication on "Embryo-fetal toxicity assessment of vonoprazan in rats and rabbits"[16] which will not be discussed in this clinical review.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed on 2/10/22 using the search terms "vonoprazan AND pregnancy," "vonoprazan and pregnancy and birth defects," "vonoprazan and pregnancy and congenital malformations," "vonoprazan and pregnancy and stillbirth," "vonoprazan AND teratogenicity" and "vonoprazan AND prematurity", "vonoprazan AND low birth weight" and "vonoprazan and pregnancy and miscarriage." No reports of adequate and well-controlled studies of vonoprazan use in pregnant women were

[16] Li, Tianyi, Qiao, Hongqun, Yue, Peng, Cai, Ming and He, Xuejun. Embryo-fetal toxicity assessment of vonoprazan in rats and rabbits. Journal of Applied Toxicology. 2018; 38 (7): 987-995.

identified. No case reports or case series were identified. Vonoprazan is not referenced in Micromedex[17].

Pregnancy- Amoxicillin

Nonclinical Experience

Reproduction studies with amoxicillin have been performed in mice and rats at doses up 2000 mg/kg (5 and 1010 times the 2 g human dose, respectively, 3 and 6 times the 3 g human dose, respectively, based on BSA comparison). There was no evidence of harm to the fetus due to amoxicillin.

Applicant's Review of Literature

At the Agency's request, the applicant performed a search on 1/11/22 of amoxicillin use in pregnant individuals in the following databases: AdisInsight: Drugs, AdisInsight: Trials, BIOSIS Previews®, COVID-19 Research, Embase®, MEDLINE®, Morressier Life Science Conference Abstracts and Posters, Publicly Available Content. No details regarding the years searched was provided. See below under "DPMH's Review of Literature" for publications identified by the applicant but previously reviewed in the DPMH 2019 review for Moxatag (amoxicillin)[1]. The applicant cited multiple publications comparing use of amoxicillin or amoxicillin-clavulanic acid (Augmentin) to other antibiotics for the treatment of a variety of causes (infections, asymptomatic bacteriuria, and preterm labor with and without rupture of membranes) during pregnancy. The majority of the 96 clinical publications identified by the applicant did not discuss pregnancy outcomes so these won't be discussed further in this review. See Table 4 in Attachment B for summaries of the additional publications identified by the applicant that have relevant maternal and fetal outcomes reported.

DPMH's Review of Literature

In 2019, DPMH reviewed Moxatag (amoxicillin),[1] the reader is referred to this review for summaries for the following publications, those also identified by the applicant are in *italics*: Anderson JT et al (2013), *Andrew MA 2007*, Briggs GG et al (2017), Buckingham M et al (1975), Cooper WO et al. (2009), *Duff P et al (1991)*, Eric M et al (2012), *Jepsen P et al (2003)*, *Lin KJ et al (2012)*, Molgaard-Nielsen D and Hviid A (2012), Muanda FT, Sheehy O, Berard A (2017), Puho EH et al. (2007), Romoren M et al (2012), Santo F et al (2011), *Thorpe PG et al. (2013*), Zarante I et al (2009), *Zareba-Szczudlik J (2017)* and Zhanel (1999). In September of 2019, the DPMH reviewer reached the following conclusions regarding the published literature and the effect of amoxicillin on pregnancy:

> While available studies cannot definitively establish the absence of risk, published epidemiological data and post-marketing case reports have not reported a consistent association with amoxicillin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when amoxicillin was used during pregnancy. Available studies have methodologic limitations, including small sample size, retrospective data collection, under-capture of non-live births, exposure misclassification, and inconsistent comparator groups.

[17] https://www.micromedexsolutions.com/micromedex2/librarian/ssl/true. Accessed 2/10/22

This reviewer searched the published literature on 2/15/22 in PubMed for the time-period covering 1/1/19 through the present regarding use of amoxicillin during pregnancy and identified several additional publications of interest. Summaries of these articles were added to Table 4 in Attachment B using blue ink.

Reviewer's Comments
The majority of the publications, many of which were randomized controlled trials, were designed to ascertain whether antibiotic therapy lessened the incidence of adverse maternal and fetal outcomes in patients with preterm labor. This was studied in two populations: pregnant women with preterm labor with premature rupture of membranes (PPROM) and pregnant women with preterm labor without premature rupture of membranes.

In patients with PPROM, the composite primary outcome (pregnancies complicated by at least one: fetal or infant death, respiratory distress, severe intraventricular hemorrhage, stage 2 or 3 necrotizing enterocolitis, or sepsis within 72 hours of birth), respiratory distress, and necrotizing enterocolitis were less frequent with antibiotic treatment. Significant pregnancy prolongation was seen with antibiotic treatment in the PPROM group.

In patients with preterm labor with intact membranes, no significant difference between groups was found in maternal outcomes (including duration of randomization-to-delivery interval, frequency of preterm delivery, and frequency of clinical chorioamnionitis and endometritis), except for the rate of cesarean section, which was significantly higher in the placebo group (28% vs. 12%). Regarding neonatal outcome, in both PPROM and patients with preterm labor with intact membranes, no significant difference was detected in neonatal death, respiratory distress syndrome, proven sepsis, and birthweight.

These findings are important but are not specific to amoxicillin since multiple different antibiotic regimens (some including amoxicillin and some without) have been found to produce the same effect. Therefore, this reviewer does not recommend any additions to the current labeling language for amoxicillin in subsection 8 for (b) (4) *products.*

Pregnancy- Clarithromycin

Nonclinical Experience
In animal reproduction studies, administration of oral clarithromycin to pregnant mice, rats, rabbits, and monkeys during the period of organogenesis produced malformations in rats (cardiovascular anomalies) and mice (cleft palate) at clinically relevant doses based on BSA comparison. Fetal effects in mice, rats, and monkeys (e.g., reduced fetal survival, body weight, body weight gain) and implantation losses in rabbits were generally considered to be secondary to maternal toxicity.

Applicant's Review of Literature
At the Agency's request, the applicant performed a search on 1/11/22 of clarithromycin use in pregnant and lactating individuals and the effects of these drugs on pregnancy in the following databases: AdisInsight: Drugs, AdisInsight: Trials, BIOSIS Previews®, COVID-19 Research, Embase®, MEDLINE®, Morressier Life Science Conference Abstracts and

Posters, Publicly Available Content. No details regarding the years searched was provided. The applicant identified two case reports with exposure to clarithromycin during pregnancy which are summarized below.

- Islam[18] et al (2016) described a 36-year-old pregnant woman diagnosed with influenza admitted with premature rupture of membranes at 29 weeks who was treated with oseltamivir, amoxicillin, clarithromycin and steroids for pneumonia. She underwent emergent cesarean section and was transferred to the ICU with an additional diagnosis of acute respiratory distress syndrome. The baby was kept under close surveillance, and it did not develop flu morbidity. Maternal condition gradually improved and 7 days after delivery patient was discharged home.
- Richard[19] et al (2021) described a 33-year-old pregnant woman who was treated for 15 days with amoxicillin, esomeprazole, clarithromycin and metronidazole for *H. pylori* eradication. Three months after treatment initiation, the patient experienced dental black stains, which were successfully treated by dental scaling but unfortunately recurred in three weeks. Fourteen months later, the same discoloration was noticed on the teeth of her 1-year- old daughter.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed on 2/10/22 using the search terms "clarithromycin and pregnancy," "clarithromycin and pregnancy and birth defects," "clarithromycin and pregnancy and congenital malformations," "clarithromycin and pregnancy and stillbirth," "clarithromycin and spontaneous abortion" clarithromycin and teratogenicity" and "clarithromycin and pregnancy and miscarriage." See Table 5 in Attachment B for summaries of the publications identified by this reviewer that have relevant maternal and fetal outcomes reported.

Reviewer's Comments

Several observational studies reported an increased risk of SAB associated with exposure to clarithromycin with hazard ratios varying from 1.56- 1.98 and relatively narrow confidence intervals. Findings with regard to MCMs were inconsistent with some studies showing no increase and other finding associations with cardiac malformations, orofacial clefts and genital malformations. Many of these associations were based on a small number of cases and had wide confidence intervals.

[18]Islam SM et al. A case of severe influenza leading to ARDS and preterm labour. Journal of Maternal-Fetal and Neonatal Medicine. 2016; 29: 285.

[19]Richard HM et al. Amoxicillin-induced 'dental stains': A case report and analysis of the French pharmacovigilance database. Fundamental and Clinical Pharmacology 35(SUPPL 1): 145.

Lactation-Vonoprazan

Nonclinical Experience
Vonoprazan and its metabolites are present in rat milk.

Reviewer's Comments
On 2/9/22, DPMH was informed by the pharm-tox team that "liver lesions" had been seen in rat pups exposed to vonoprazan during lactation only. The applicant conducted additional nonclinical studies to try to investigate these changes. DPMH recommends including these findings in Section 8 and recommends a PMR for a clinical lactation study to determine if vonoprazan is present in clinically important quantities in human milk.

Applicant's Review of Literature
The original submission on 9/3/21 for the (b) (4) Triple Pak NDA under "labeling history" included a review and summary of published information on the use of vonoprazan in lactating individuals in the following databases: AdisInsight: Drugs, AdisInsight: Trials, BIOSIS Previews®, COVID-19 Research, Embase®, MEDLINE®, Morressier Life Science Conference Abstracts and Posters, Publicly Available Content. No publications were identified regarding the use of vonoprazan during lactation.

DPMH Review of Literature
DPMH conducted a search of *Medications and Mother's Milk*[20], the Drugs and Lactation Database (LactMed),[21] Micromedex[15], and of published literature in PubMed using the search terms "vonoprazan and lactation" and "vonoprazan and breastfeeding." No studies of vonoprazan use in lactating women were identified. No observational studies or case reports of vonoprazan use in lactating women were found. Vonoprazan is not referenced in *Medications and Mother's* Milk[18] or in LactMed[19].

Lactation-Amoxicillin

Nonclinical Experience
Data from animal studies regarding the presence of amoxicillin in rat milk are not reported (since they are no longer relevant) as there is a published human clinical lactation study that reports that amoxicillin is present in human milk.

Applicant's Review of Literature
At the Agency's request, the applicant performed a search on 1/11/22 of amoxicillin use in lactating individuals in the following databases: AdisInsight: Drugs, AdisInsight: Trials, BIOSIS Previews®, COVID-19 Research, Embase®, MEDLINE®, Morressier Life Science Conference Abstracts and Posters, Publicly Available Content. No details regarding the years searched was provided. See below under "DPMH's Review of Literature" for publications identified by the applicant but previously reviewed in the DPMH 2019 review for Moxatag

[20] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 422-423.
[21] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

(amoxicillin)[1]. The following publication was identified by the applicant as relevant to use of amoxicillin during pregnancy and is summarized below.

- Nahum[22] et al (2006) reviews the risks and pharmacokinetic considerations for 11 broad-spectrum antibiotics that can be used to treat routine and life-threatening infections during pregnancy and lactation. The teratogenic potential in humans ranged from "none" (penicillin G and VK) to "unlikely" (amoxicillin, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, and rifampin) to "undetermined" (clindamycin, gentamicin, and vancomycin). Assessments were based on "good data" (penicillin G and VK), "fair data" (amoxicillin, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, and rifampin), "limited data" (clindamycin and gentamicin), and "very limited data" (vancomycin).

DPMH Review of Literature

In 2019, DPMH reviewed Moxatag (amoxicillin),[1] the reader is referred to this review for summaries for the following publications, those also identified by the applicant are in *italics*: *Kafetziz[23] et al (1981),* Ito[24], et al. (1993) and *Benyamini[25]and Merlob (2005).* On 2/10/22, DPMH conducted a search of *Medications and Mother's Milk*[26], the Drugs and Lactation Database (LactMed),[27] Micromedex[11], and of published literature in PubMed using the search terms "amoxicillin and lactation" and "amoxicillin and breastfeeding" for the time-period of 1/1/19 through the present. No additional relevant publications were identified.

Amoxicillin is referenced in *Medications and Mother's* Milk[7]. The author describes the lactation study findings by Kafetziz[21], previously reviewed by DPMH[1] and calculated from the data, a relative infant dose (RID)[7]of 1%. Hale concludes that based on the previously mentioned study, amoxicillin is compatible with breastfeeding.

Amoxicillin is referenced in LactMed[8]. The authors describe the lactation study conducted by Kafetziz[21], and calculated from the data that an exclusively breastfed infant would be expected to receive a maximum daily dosage of about 0.1 mg/kg of amoxicillin with a maternal dose of 500 mg three times daily, which amounts to 0.25 to 0.5% of a typical infant amoxicillin dosage. LactMed summarizes that the limited information indicates that amoxicillin produces low levels in milk that are not expected to cause adverse effects in infants and that amoxicillin is acceptable for use in nursing mothers. Diarrhea and thrush have been reported in breastfed infants, but these effects have not been adequately evaluated for an association with exposure to the drug through breastmilk.

---

[22] Nahum GG et al. Antibiotic use in pregnancy and lactation - What is and is not known about teratogenic and toxic risks. Obstetrics & Gynecology. 2006; 107(5): 1120-1138.

[23] Kafetzis DA et al. Passage of cephalosporins and amoxicillin into the breastmilk. Acta Paediatr Scand, 1981;70:285-288.

[24] Ito S et al. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol, 1993; 168:1393-1399.

[25] Benyamini L, Merlob P. The safety of amoxicillin/clavulanic acid and cefuroxime during lactation. Ther Drug Monit. 2005; 27:499-502.

[26] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 422-423.

[27] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Lactation- Clarithromycin

Nonclinical Experience
No data available for clarithromycin use in lactating animals.

Applicant's Review of Literature
At the Agency's request, the applicant performed a search on 1/11/22 of clarithromycin use in lactating individuals in the following databases: AdisInsight: Drugs, AdisInsight: Trials, BIOSIS Previews®, COVID-19 Research, Embase®, MEDLINE®, Morressier Life Science Conference Abstracts and Posters, Publicly Available Content. No details regarding the years searched was provided. See below under "DPMH Review of Literature" for one publication identified by the applicant which was previously reviewed by DPMH and a new study by Kul[29] which is cited by LactMed[25] and is summarized below under the entry for that database.

DPMH Review of Literature
In 2013, DPMH reviewed the lactation literature for Biaxin (clarithromycin),[2] the reader is referred to this review for summaries for the following publications: those also identified by the applicant are in *italics*: Sedlmayr[28] et al (1993) and *Goldstein[29] et al (2009).*

DPMH conducted a search of Medications and Mother's Milk[24], the Drugs and Lactation Database (LactMed)[25], Micromedex[11], and of published literature in PubMed for the time period 1/1/13 through the present using the search terms "clarithromycin and lactation" and "clarithromycin and breastfeeding." No new studies or case reports were located beyond those discussed above and below for clarithromycin use in lactating women.

Clarithromycin is referenced in Medications and Mother's Milk[24]. The author cites the study by Sedlmayr[26]

> In a study of 12 mothers receiving 250 mg twice daily, the Cmax occurred at 2.2 hours and was reported to be 0.85 mg/L. The estimated average dose of clarithromycin via milk was reported to be 150 ug/kg/day, or 2% of the maternal dose. Clarithromycin is probably compatible with breastfeeding.

Clarithromycin is referenced in LactMed.[8] The authors "Summary of Use during Lactation" states

> Because of the low levels of clarithromycin in breastmilk and safe administration directly to infants, it is acceptable in nursing mothers. The small amounts in milk are unlikely to cause adverse effects in the infant. Monitor the infant for possible effects on the gastrointestinal flora, such as diarrhea, candidiasis (thrush, diaper rash). Unconfirmed epidemiologic evidence indicates that the risk of infantile hypertrophic pyloric stenosis might be increased by maternal use of macrolide antibiotics during the first two weeks of breastfeeding, but others have questioned this relationship.

[28]Sedlmayr et al. Clarithromycin, a new macrolide antibiotic. Effectiveness in puerperal infections and pharmacokinetics in breast milk. Geburtshilfe Frauenheilkd.1993; 53: 488-91.
[29] Goldstein et al. The safety of macrolides during lactation. 2009; 4:197-200.

Under "Drug Levels" the LactMed authors also describe the study by Sedlmayr[26]and note that

> …an exclusively breastfed infant would receive an estimated average of about 136 mcg/kg daily of drug plus metabolite with a maternal dosage of 500 mg daily. This dosage is less than 1% of the recommended pediatric (<6 months) dosage and is about 1.7% of the maternal weight-adjusted dosage.

The LactMed authors also describe lactation information from a new study by Kul[30] et al (2021) of a single woman given a 500 mg dose of clarithromycin

> Ten milk samples were collected over the following 24 hours. The peak milk concentration of 3.660 mg/L was obtained at 2.5 hours after the dose. The average milk concentration was 0.769 mg/L and the half-life in milk was 3.86 hours.

Reviewer's Comments
The clinical pharmacology team was asked to evaluate whether the new study from 2021 by Kul[29] should be included in labeling for subsection 8.2. This study by Kul[29] yielded higher values for the peak milk concentration (3.660 mg/L was obtained at 2.5 hours after the dose) than the study currently cited in subsection 8.2 of clarithromycin labeling by Sedlmayr et al (1993) which reported a peak milk concentration of 0.85 mg/L at 2.2 hours after the dose. However, the Kul[29] study reported findings from 10 milk samples taken over time from a single individual. At the time this review was finalized clinical pharmacology was still assessing the study.

Females and Males of Reproductive Potential-Vonoprazan

Nonclinical Experience
Vonoprazan at oral doses up to 300 mg/kg/day in rats (approximately 133 times the MRHD based on AUC from the same dose administered in a separate study with nonpregnant animals) 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.

Applicant's Review of Literature
The applicant did not identify any published literature regarding vonoprazan and effects on fertility.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed regarding vonoprazan and its effects on fertility and found no relevant articles.

[30] Kul A et al. Pharmacokinetic study of clarithromycin in human breast milk by UPLC-MS/MS. J Pharm Biomed Anal. 2021;208:114438.

Females and Males of Reproductive Potential-Amoxicillin

Nonclinical Experience
In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 1.6 times the human dose based on body surface area (mg/m^2)).

Applicant's Review of Literature
The applicant did not identify any published literature regarding amoxicillin and effects on fertility.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed regarding amoxicillin and its effects on fertility and found no relevant articles.

Females and Males of Reproductive Potential-Clarithromycin

Nonclinical Experience
Testicular atrophy occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose (on a BSA comparisons).

From Nonclinical Toxicology (13.1)
Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were twice the human serum levels.

Testicular atrophy occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose (on a BSA comparisons).

Applicant's Review of Literature
The applicant did not identify any published literature regarding clarithromycin and effects on human fertility.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed regarding clarithromycin and its effects on human fertility and found no relevant articles.

DISCUSSION AND CONCLUSIONS

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 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 the vonoprazan component of (b) (4) products at relevant doses. See proposed labeling for recoommended 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.

Amoxicillin

Though some new publications regarding the use of amoxicillin in pregnant women were identified, none of the information suggested a need for additions to the currently approved language for amoxicillin in Section 8.1.

However, this reviewer recommends removing the "Human Data" subsection" for amoxicillin labeling since it does not provide any additional information beyond what is conveyed in the risk summary statement.

Clarithromycin

Currently approved labeling for Biaxin (clarithromycin) from 2019, already carries a Warnings and Precautions for embryo-fetal toxicity based on animal findings. There is no human data section in the currently approved Biaxin (clarithromycin) labeling.

This reviewer finds sufficient evidence in the published literature of an increase in the rate of spontaneous abortion/ miscarriage (SAB) to include this finding in labeling. Consistently across multiple studies an increase in SAB has been noted. See Table 5 in Attachment B for summaries of the publications. The situation is less clear with the rate of major congenital malformations/birth defects (MCM). Here the findings are inconsistent. For now, erring on the side of caution, DPMH recommends including risk of SAB in labeling. See proposed labeling for recoommended language.

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. For both amoxicillin and clarithromycin, there is data from lactation studies, so no PMR is needed for those products.

Amoxicillin

Data from a published clinical lactation study reports that amoxicillin is present in human milk. Lactation experts have concluded that based on low levels in human milk, amoxicillin use is compatible with breastfeeding. Diarrhea and thrush have been reported in breastfed infants.

Clarithromycin

Based on published human lactation studies, clarithromycin is present in human milk at low levels (less than 2% of the maternal weight-adjusted dose). Rash, diarrhea, loss of appetite and somnolence have been reported in breastfed infants. One additional new lactation report identified in the published literature from 2021 by Kul[29] *et al* reports a somewhat higher level of clarithromycin in a single patient given clarithromycin. Clinical pharmacology is still assessing this study to determine whether or not to add the results to labeling. See final approved labeling for the chosen language.

Females and Males of Reproductive Potential

Vonoprazan and amoxicillin did not have any worrisome animal findings with regard to effects on fertility. (b) (4) This reviewer did not find any additional information in the published human literature on this topic. PLLR regulation recommends including in this subsection whether or not the findings were reversible. The Nonclinical reviewer advised that this information is proprietary and therefore cannot be added to labeling for this product since the applicant does not have rights to this data.

LABELING RECOMMENDATIONS

DPMH revised the Highlights and subsections 5.6, 8.1, 8.2, 8.3, and section 17 of (b) (4) Triple Pak labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed (b) (4) TRIPLE PAK Pregnancy and Lactation Labeling

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Attachment A

Current State of Labeling for Amoxicillin- Amoxil (2016)

8.1 Pregnancy
Teratogenic Effects:
Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 2000 mg/kg (3 and 6 times the 3 g human dose, based on body surface area). There was no evidence of harm to the fetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, amoxicillin should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery
Oral ampicillin is poorly absorbed during labor. It is not known whether use of amoxicillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood of the necessity for an obstetrical intervention.

8.3 Nursing Mothers
Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

Current State of Labeling for Clarithromycin- Biaxin (2019)

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------Warnings and Precautions----------

- Embryo-Fetal Toxicity: Based on animal findings, BIAXIN is not recommended for use in pregnant women except in clinical circumstances where no alternative therapy is appropriate (5.7)

FULL PRESCRIBING INFORMATION
5.7 Embryo-Fetal Toxicity

Based on findings from animal studies, BIAXIN is not recommended for use in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If BIAXIN is used during pregnancy, or if pregnancy occurs while the patient is taking this drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin demonstrated adverse effects on pregnancy outcome and/or embryo fetal development, including fetal malformations, in pregnant animals administered oral clarithromycin *[see Use in Specific Populations (8.1)]*.

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on findings from animal studies, BIAXIN is not recommended for use in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking BIAXIN, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.7)]*.

Limited data from a small number of published human studies with Biaxin use during pregnancy are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, administration of oral clarithromycin to pregnant mice, rats, rabbits, and monkeys during the period of organogenesis produced malformations in rats (cardiovascular anomalies) and mice (cleft palate) at clinically relevant doses based on body surface area comparison. Fetal effects in mice, rats, and monkeys (e.g., reduced fetal survival, body weight, body weight gain) and implantation losses in rabbits were generally considered to be secondary to maternal toxicity *(see Data).*

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

Data

Animal Data

Animal reproduction studies were conducted in mice, rats, rabbits, and monkeys with oral and intravenously administered clarithromycin. In pregnant mice, clarithromycin was administered during organogenesis (gestation day [GD] 6 to 15) at oral doses of 15, 60, 250, 500, or 1000 mg/kg/day. Reduced body weight observed in dams at 1000 mg/kg/day (3 times the maximum recommended human dose [MRHD] based on body surface area comparison) resulted in reduced survival and body weight of the fetuses. At ≥ 500 mg/kg/day, increases in the incidence of post-implantation loss and cleft palate in the fetuses were observed. No adverse developmental effects were observed in mice at ≤ 250 mg/kg/day (≤ 1 times MRHD based on body surface area comparison).

In pregnant Sprague Dawley rats, clarithromycin was administered during organogenesis (GD 6 to 15) at oral doses of 15, 50, or 150 mg/kg/day. Reductions in body weight and food consumption was observed in dams at 150 mg/kg/day. Increased resorptions and reduced body weight of the fetuses at this dose were considered secondary to maternal toxicity. Additionally, at 150 mg/kg/day (1 times MRHD based on body surface area comparison), a low incidence of cardiovascular anomalies (complete situs inversus, undivided truncus, IV septal defect) was observed in the fetuses. Clarithromycin did not cause adverse developmental effects in rats at 50 mg/kg/day (0.3 times MRHD based on body surface area comparison). Intravenous dosing of clarithromycin during organogenesis in rats (GD 6 to 15) at 15, 50, or 160 mg/kg/day was associated with maternal toxicity (reduced body weight, body-weight gain, and food consumption) at 160 mg/kg/day but no evidence of adverse developmental effects at any dose (≤ 1 times MRHD based on body surface area comparison).

In pregnant Wistar rat, clarithromycin was administered during organogenesis (GD 7 to 17) at oral doses of 10, 40, or 160 mg/kg/day. Reduced body weight and food consumption were observed in dams at 160 mg/kg/day but there was no evidence of adverse developmental effects at any dose (≤ 1 times MRHD based on body surface area comparison).

In pregnant rabbits, clarithromycin administered during organogenesis (GD 6 to 18) at oral doses of 10, 35, or 125 mg/kg/day resulted in reduced maternal food consumption and decreased body weight at the highest dose, with no evidence of any adverse developmental effects at any dose (≤ 2 times MRHD based on body surface area comparison). Intravenously administered clarithromycin to pregnant rabbits during organogenesis (GD 6 to 18) in rabbits at 20, 40, 80, or 160 mg/kg/day (≥ 0.3 times MRHD based on body surface area comparison) resulted in maternal toxicity and implantation losses at all doses.

In a reproductive toxicology study in rats administered oral clarithromycin late in gestation through lactation (GD 17 to post-natal day 21) at doses of 10, 40, or 160 mg/kg/day (≤ 1 times MRHD based on body surface area comparison), reductions in maternal body weight and food consumption were observed at 160 mg/kg/day. Reduced body-weight gain observed in offspring at 160 mg/kg/day was considered secondary to maternal toxicity. No adverse developmental effects were observed with clarithromycin at any dose tested.

8.2 Lactation

Risk Summary

Based on limited human data, clarithromycin and its active metabolite 14-OH clarithromycin are present in human milk at less than 2% of the maternal weight-adjusted dose (*see Data*). In a separate observational study, reported adverse effects on breast-fed children (rash, diarrhea, loss of appetite, somnolence) were comparable to amoxicillin (*see Data*). No data are available to assess the effects of clarithromycin or 14-OH clarithromycin on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for BIAXIN and any potential adverse effects on the breast-fed child from BIAXIN or from the underlying maternal condition.

Data

Human

Serum and milk samples were obtained after 3 days of treatment, at steady state, from one published study of 12 lactating women who were taking BIAXIN 250 mg orally twice daily. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively human milk fed infant would receive an estimated average of 136 mcg/kg/day of clarithromycin and its active metabolite, with this maternal dosage regimen. This is less than 2% of the maternal weight-adjusted dose (7.8 mg/kg/day, based on the average maternal weight of 64 kg), and less than 1% of the pediatric dose (15 mg/kg/day) for children greater than 6 months of age.

A prospective observational study of 55 breastfed infants of mothers taking a macrolide antibacterial (6 were exposed to clarithromycin) were compared to 36 breastfed infants of mothers taking amoxicillin. Adverse reactions were comparable in both groups. Adverse reactions occurred in 12.7% of infants exposed to macrolides and included rash, diarrhea, loss of appetite, and somnolence.

8.3 Females and Males of Reproductive Potential

Males

Administration of clarithromycin resulted in testicular atrophy in rats, dogs and monkeys *[see Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING INFORMATION

Provide the following instructions or information about BIAXIN to patients:

Embryo-Fetal Toxicity

Advise females of reproductive potential that that if pregnancy occurs while taking this drug, there is a potential hazard to the fetus *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)]*.

Attachment B

Table 4: Additional Studies of Amoxicillin Use in Pregnancy Identified by the Applicant/ Identified by the Reviewer

Citation	#of Women Treated	Mean Gestational Age (weeks)	Drug (s)/Dose(s)	Indication	Outcomes
Tampakoudis[1] et al. 1996	75	32	Augmentin 1.2 grams IV q 8 hours for 3-4 days followed by oral at 625mg q 8 hours till labor	premature rupture of membranes (PROM)	-61 had uncomplicated course with a mean 11.4+/-5.7 days to delivery -14 developed chorioamnionitis of whom 5 had fetal/infant death (these five had mean gestational age ≈ 24 weeks)
Mercer[2] et al 1997 Randomized Controlled Trial (RCT)	614	24-32	Intravenous (IV) ampicillin (Amp) 2 grams q 6 hours + erythromycin (ER) 250 mg q 6 hours for 48 hours followed by oral amoxicillin (Amox) 250 mg q 8 hours and ER base 333mg q 8 hours for 5 days vs placebo	preterm premature rupture of membranes (PPROM)	Primary outcome (pregnancies complicated by at least one: fetal or infant death, respiratory distress, severe intraventricular hemorrhage, stage 2 or 3 necrotizing enterocolitis, or sepsis within 72 hours of birth), respiratory distress, and necrotizing enterocolitis were less frequent with antibiotics. Significant pregnancy prolongation was seen with antibiotics.

[1] Tampakoudis P et al. Prophylactic administration of amoxicillin and clavulanic acid in pregnant women with premature rupture of the membranes. Journal of Chemotherapy. 1996; 8(4): 290-294.

[2] Mercer BM et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. JAMA. 1997;278(12):989-995.

Attachment B

Table 4: Additional Studies of Amoxicillin Use in Pregnancy Identified by the Applicant/ Identified by the Reviewer

Citation	#of Women Treated	Mean Gestational Age (weeks)	Drug (s)/Dose(s)	Indication	Outcomes
Oyarzun[3] et al 1998 RCT	196	22-36	Amox + ER vs placebo	Preterm labor, Intact membranes	No significant difference between both groups was found in maternal outcomes, including duration of randomization-to delivery interval, frequency of preterm delivery, and frequency of clinical chorioamnionitis and endometritis. Rate of cesarean section was significantly higher in the placebo group (28% vs. 12%). Regarding neonatal outcome, no significant difference was detected between both groups in neonatal death, respiratory distress syndrome, proven sepsis, and birthweight. Suspected sepsis was significantly more frequent in the placebo group (6/90 vs. 0/78).
Kenyon[4] et al. 2001 RCT Oracle I	4826	Not reported (NR) In abstract	250 mg ER (n=1197), 325 mg Augmentin (n=1212), Both (n=1192), or placebo (n=1225) four times daily for 10 days or until delivery.	PPROM	Primary outcome (PO) = a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasound before discharge from hospital Fewer had the PO in the ER group (151 of 1190 (12.7%) vs 186 of 1225 (15.2%), p=0.08) than in the placebo group. Significantly fewer had the PO in the ER group (125 of 1111 (11.2%) vs 166 of 1149 (14.4%), p=0.02) Augmentin only and Augmentin + ER had no benefit over placebo

[3]Oyarzun E et al. Antibiotic treatment in preterm labor and intact membranes: A randomized, double-blinded, placebo-controlled trial. Journal of Maternal-Fetal Medicine. 1998; 7(3): 105-110.

[4] Kenyon SL et al. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: The ORACLE I randomized trial. Lancet (North American Edition). 2001; 357(9261): 979-988.

Attachment B

Table 4: Additional Studies of Amoxicillin Use in Pregnancy Identified by the Applicant/ Identified by the Reviewer

Citation	#of Women Treated	Mean Gestational Age (weeks)	Drug (s)/Dose(s)	Indication	Outcomes
Kenyon[5] et al 2001 RCT ORACLE II	6295	NR In abstract	250 mg erythromycin (n=1611), 325 mg Augmentin(n=1550), both (n=1565), or placebo (n=1569) four times daily for 10 days or until delivery	Preterm labor, Intact membranes	PO = same as Oracle I None of the trial antibiotics was associated with a lower rate of the PO than placebo (ER 90 (5.6%), Augmentin 76 (5.0%), both 91 (5.9%), vs placebo 78 (5.0%)). However, antibiotic prescription was associated with a lower occurrence of maternal infection.
Keuchkerian[6] Et al RCT 2005	96	24 - 34	Amoxicillin Sulbactam	Preterm labour, Intact membranes	PO = prematurity There were no significant statistical differences between antibiotics and placebo group in prematurity (RR:1.04, 95% CI: 0.59, 1.84), prolongation of pregnancy (WMD:0.23, 95% CI: -0.96, 1.42) and other perinatal outcomes.
Kenyon[7] et al 2008 7-year follow up ORACLE 1	Children born to 4148 women	NR in abstract	250 mg ER (n=1197), 325 mg Augmentin (n=1212), Both (n=1192), or placebo (n=1225) four times daily for 10 days or until delivery.	PPROM	Primary Outcome = Functional impairment (FI) = presence of any level of FI (severe, moderate, or mild) on the mark III Multi-Attribute Health Status classification system. There was no difference in % of children with any FI after prescription of ER, with or without Augmentin, compared with those born to mothers who received no ER (594 [38.3%] of 1551 children vs 655 [40.4%] of 1620; odds ratio 0.91, 95% CI 0.79-1.05) or after prescription of Augmentin, with or without ER, compared with those born to mothers who received no Augmentin (645 [40.6%] of 1587 vs 604 [38.1%] of 1584; 1.11, 0.96-1.28)

[5] Kenyon SL et al. Broad-spectrum antibiotics for spontaneous preterm labour: The ORACLE II randomized trial. Lancet (North American Edition).2001; 357(9261): 989-994.

[6] Keuchkerian SE et al. Effect of amoxicillin sulbactam in threatened preterm labour with intact membranes: a randomized controlled trial. European journal of obstetrics, gynecology, and reproductive biology. 2005; 119(1): 21-26.

[7] Kenyon SL.et al. Childhood outcomes after prescription of antibiotics to pregnant women with preterm

Attachment B

Table 4: Additional Studies of Amoxicillin Use in Pregnancy Identified by the Applicant/ Identified by the Reviewer

Citation	#of Women Treated	Mean Gestational Age (weeks)	Drug (s)/Dose(s)	Indication	Outcomes
Muller[8] et al 2008	17	NR In abstract	amoxicillin (2 g initially and 1 g subsequently)	PPROM	The pharmacokinetics (PK) was described by a 3-compartment model. There was little variability between patients. The PK of amoxicillin in pregnant patients with PPROM is similar to nonpregnant individuals.
Muller[9] et al 2008	34	NR In abstract	amoxicillin	Healthy pregnant women during labor	The peripheral distribution volume of amoxicillin in pregnant women during labour and immediately post-partum is decreased. However, these changes are not clinically relevant and do not warrant deviations from the recommended dosing regimen for amoxicillin during labour in healthy pregnant patients.
Daniel[10] et al 2019 Retrospective cohort study	101,615 pregnancies 6919 (6.8%) Exposed to amox	NR in abstract	1045 exposed to amox alone 6041 exposed to Augmentin	Multiple	-Adjusted for mother's age, ethnicity (Bedouin vs Jewish), parity, diabetes mellitus, lack of perinatal care, and the year of birth -Exposure to amox and Augmentin during the first TM of pregnancy was not associated with an increased risk of major congenital malformations.

rupture of the membranes: 7-year follow-up of the ORACLE I trial. Lancet (North American Edition). 2008; 372(9646): 1310-1318.

[8] Muller AE et al. Amoxicillin pharmacokinetics in pregnant women with preterm premature rupture of the membranes. American Journal of Obstetrics and Gynecology. 2008; 198(1): Article No.: 108.e101.

[9] Muller AE et al. The influence of labour on the pharmacokinetics of intravenously administered amoxicillin in pregnant women. British Journal of Clinical Pharmacology. 2008; 66(6): 866-874.

[10] Daniel s et al. The safety of amoxicillin and clavulanic acid use during the first TM of pregnancy. Br J Clin Pharmacol. 2019; 85:2856–2863.

Attachment B

Table 4: Additional Studies of Amoxicillin Use in Pregnancy Identified by the Applicant/ Identified by the Reviewer

Citation	#of Women Treated	Mean Gestational Age (weeks)	Drug (s)/Dose(s)	Indication	Outcomes
Chatzakis[11] C et al 2020 Meta-analysis of RCT	20 studies 7169 patients	NR in abstract	Varied	Multiple	-For the outcome of chorioamnionitis, amp/sulbactam + augmentin (RR, 0.32 (95% CI, 0.12–0.92)), ER+ amp+ amox (RR, 0.71 (95% CI, 0.55–0.92)) were superior to placebo. -For respiratory distress syndrome, ER+ amp+ amox (RR, 0.83 (95% CI, 0.69–0.99)) were effective. - None of the antibiotics appeared significantly more effective than placebo in reducing the rates of neonatal death, perinatal death and necrotizing enterocolitis.
Fitzgibbon[12] et al 2021 Retrospective	78	NR in abstract	ER (historical control) vs Amox IV for 48 hours followed by oral Amox X 5 days	PPROM	PO = latency (between membrane rupture and delivery) There was a longer latency to delivery for those prescribed Amox (median = 5.5 days), compared with ER (median = 2 days, $p < .001$). RCT needed.

Source: Reviewer's Table

[11] Chatzakis C et al. Effect on perinatal outcome of prophylactic antibiotics in preterm prelabor rupture of membranes: network meta-analysis of randomized controlled trials. Ultrasound Obstet Gynecol 2020; 55: 20–31.

[12] Fitzgibbon AL et al. Erythromycin compared to amoxicillin and azithromycin for antimicrobial prophylaxis for preterm premature rupture of the membranes: a retrospective study. Journal of Obstetrics and Gynecology. 2021; 41(4): 569-572.

Attachment B

Table 5: Studies of Clarithromycin Use in Pregnancy Identified by the Applicant/ Identified by the Reviewer

Citation	# of Women/ Infants	Mean Gestational Age (weeks)	Dose(s)	Indication	Outcomes/Comments
Einarson[13] et al 1998 Prospective, controlled observational design	157 exposed-clarithromycin (clarith) versus (vs) 157 control[14]	Not reported (NR) except that 122 were 1st TM (TM)	NR	Multiple	- No significant differences found between the two groups in the rates of major [2.3 versus 1.4% for major (p = 0.86)]and minor [5.4 versus 4.9% for minor (p = 0.96)] malformations. -Spontaneous abortion (SAB) rates in the exposed group were significantly different, higher (14%) than in the control group (7%) (p = 0.04).
Drinkard[15] et al 2001 Retrospective design, used linked claims data and medical records	143 mothers exposed to clarith (149 infants)	1st TM	NR	NR	-5 infants with major congenital malformations (MCM), 3 with minor malformations, and 4 with undescended testicles (likely to resolve with time) - Observed rate of 3.4% (95% CI, 0.5, 6.3) for MCMs was not statistically significantly different compared to an expected rate of 2.8% based on earlier national data.
Bar-Oz[16] et al 2008 Prospective, multi-center observational design	161 exposed to macrolides (45 to clarith) vs 213 in control I[14] vs 740 in control II[17]	Not reported (NR) except that 118 were 1st TM	300-500 mg for 7 days	Multiple	-The rate of MCM in the study group was 4.1% compared to 2.1% in the other antibiotics exposed group (OR = 1.41, 95% CI 0.47– 4.23) and 3.0% in the non-teratogens exposed group. - There was not a statistically significant difference in the rate of MCM for live birth between the groups 4.1% in the macrolides exposed vs. 3.0% in the non-teratogens exposed group (odds ratio 1.41, 95% CI 0.47–4.23).

[13] Einarson A et al. A Prospective Controlled Multicentre Study of Clarithromycin in Pregnancy. American Journal of Perinatology. 1998;15(9):523-525.
[14] Control/Control I were pregnant women who recieved “nonteratogenic” antibiotics
[15] Drinkard CR et al. Postmarketing Surveillance of Medications and Pregnancy Outcomes: Clarithromycin and Birth Malformations. Pharmacoepidemiology and Drug Safety. 2001;9: 549-556.
[16]Bar-Oz B et al. Pregnancy outcome after gestational exposure to the new macrolides: A prospective multi-center observational study.
[17] Control II was pregnant women who recieved “other nonteratogenic medications” (not antibiotics)

Citation	# of Women/ Infants	Mean Gestational Age (weeks)	Dose(s)	Indication	Outcomes/Comments
Bar-Oz[18] et al 2012 Prospective, multi-center observational design	608 exposed to macrolides (255 to clarith) vs 773[17] in control II	Not reported (NR) except that 192 exposed to clarith were 1st TM	500 mg clarith X 3-7 days	Multiple	-No significant difference in the rate of MCM was found between the study group and the comparison group (3.4% vs 2.4%; p = 0.36; odds ratio (OR) 1.42; 95% CI 0.70, 2.88) or in the rate of cardiovascular malformations (1.6% vs 0.9%; p = 0.265; OR 1.91; 95% CI 0.63, 5.62).
Anderson[19] et al 2013 Register-based cohort design	931 504 pregnancies (705 837 live births, 77 553 SAB, and 148 114 induced abortions). 401 with exposure- clarith	Not reported (NR) except that 192 exposed to clarith were 1st TM	Multiple	Multiple	-Among 931 504 pregnancies in Denmark from 1997-2007, 77 553 (8.3%) had SAB, 148 114 (15.9%) had induced abortions and 705 837 (75.8%) had live births. -40 (10.0%) exposed to clarith had a SAB, the hazard ratio (HR) was 1.56 (CI95% 1.14–2.13). There was no increased hazard of having a SAB when being exposed to penicillin or erythromycin. -9 (3.6%) among the live born exposed to clarith had offspring with MCM, there was no increased prevalence (OR = 1.03 (CI95% 0.52–2.00) of having offspring with MCM after exposure to clarith.
Cardaropoli[20] et al 2014 Literature review (LR) of Helicobacter (H) *pylori* and pregnancy	Not applicable (NA)	NA	NA	NA	-H. pylori seems to be associated with hyperemesis gravidarum, a severe form of nausea and vomiting during pregnancy… H. pylori infection and pregnancy-related disorders was mainly focused on iron deficiency anemia, thrombocytopenia, fetal malformations, miscarriage, pre-eclampsia and fetal growth restriction… hormonal and immunological changes occurring during pregnancy could activate latent H. pylori with a negative impact not only on maternal health (nutritional deficiency, organ injury, death), but also on the fetus (insufficient growth, malformation, death).

[18] Bar-Oz B et al. The Outcomes of Pregnancy in Women Exposed to the New Macrolides in the First TM A Prospective, Multicentre, Observational Study. Drug Safety. 2012; 35 (7): 589-598.

[19] Andersen JT et al. (2013) Clarithromycin in Early Pregnancy and the Risk of Miscarriage and Malformation: A Register Based Nationwide Cohort Study. PLoS ONE 8(1): e53327.

[20]Cardaropoli S et al. Helicobacter pylori and pregnancy-related disorders. World J Gastroenterol 2014 January 21; 20(3): 654-664.

Citation	# of Women/ Infants	Mean Gestational Age (weeks)	Dose(s)	Indication	Outcomes/Comments
Omranipoor[21] et al 2020 Systematic review and meta-analysis	12 studies (8 prospective (P) cohort, 4 population-based (PB) case-control) 1,084,792 participants and 7015 cases of SAB	NA	NA	NA	-Use of macrolides (RR: 1.42; 95% CI 1.04, 1.93), quinolones (RR: 2.48; 95% CI 1.46, 4.20), and tetracyclines (RR: 2.57; 95% CI 1.95, 3.38) during pregnancy were significantly associated with SAB. -Clarithromycin use during pregnancy had a stronger association with SAB (RR: 1.98; 95% CI 1.46, 2.70). Sensitivity analysis demonstrated the consistency of the results, indicating that the meta-analysis model was robust.
Fan[22] et al 2020 PB cohort design	104,605 children with mothers exposed to macrolides vs penicillin vs control (siblings)	1st TM	Multiple	Multiple	-186 MCM in 8632 (2.2%) children of mothers exposed to macrolides vs 1666 MCM in 95973 (1.7%) mothers exposed to penicillins (adjusted risk ratio (RR) = 1.55, 95% confidence interval (CI) 1.19-2.03), for cardiovascular malformations RR = 1.62, 1.05-2.51, for genital malformations RR = 1.58, 1.14 to 2.19 (mainly hypospadias). No statistically significant associations were found for other system-specific malformations or for neurodevelopmental disorders. Findings were robust to sensitivity analyses. Findings for clarithromycin had wide confidence intervals.
Leke[23] et al 2021 Case-malformed control design	307 exposed to macrolides out of 145,936 babies with a diagnosis of MCM from 15 registries vs controls, 9 million births	1st TM	NR	Multiple	-Adjusted odds ratio (AOR) for overall congenital heart defects (CHD) not significantly raised, also not raised for any specific macrolide. - Risk of atrioventricular septal defect was significantly raised with exposure to any macrolide (AOR 2.98; 95 %CI: 1.48–6.01), for clarith (based on 2 cases) it was AOR 6.85; 95 %CI 1.41–33.32 -Clarith was also associated with orofacial clefts (based on 8 cases) with an AOR of 2.94; 95 %CI 1.04–8.30.

Source: Reviewer's Table

[21] Omranipoor A et al. Association of antibiotics therapy during pregnancy with spontaneous miscarriage: a systematic review and meta-analysis. Archives of Gynecology and Obstetrics (2020) 302:5–22.

[22] Fan H et al. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population-based cohort study. BMJ 2020;368:m331 http://dx.doi.org/10.1136/bmj.m331.

[23] Fan AZ et al. Macrolide and lincosamide antibiotic exposure in the first TM of pregnancy and risk of congenital anomaly: A European case-control study. Reproductive Toxicology. 2021;100: 101-108.

Table 6: Summary of Clinical Trial Cases with Known Pregnancy Outcome

Patient I.D. /Case #	Vonoprazan Dose (mono) / Combination regimen (list additional therapy)	Exposure Duration	Exposure Period*	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome**	Concomitant Medications (If Major / Minor congenital malformation (CM)	Comments (Description of CMs)
(b) (6)	TAK-438 vs Lansoprazole (Lan) / Tablet, Tak-438 vs Lan/Tablet Placebo/Capsule-received Vonoprazan (Von) 20mg	(b) (6)	1st TM	Elective abortion (TAB)	Not applicable (N/A)	N/A	N/A
	TAK-438 vs Lan/ Capsule, Placebo / Tablet received Lan 30mg		1st TM	Live Birth	None	N/A	N/A
	TAK-438 vs Lan / Capsule UNK [bid]		1st TM	Spontaneous abortion (SAB)	SAB	N/A	N/A
(See Table 2 for narrative)	TAK-438 vs Lan / Capsule-received Lan 30 mg UNK [qd] Placebo / Tablet UNK [bid] Placebo / Tablet UNK [qd] Amoxicillin (amox) / UNK UNK [1 gram-UNK] Clarithromycin (Clarith) / UNK UNK [500 mgUNK] Bismuth Potassium Citrate / UNK UNK [600 mgUNK]						

Patient I.D. /Case #	Vonoprazan Dose (mono) / Combination regimen (list additional therapy)	Exposure Duration	Exposure Period*	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome**	Concomitant Medications (If Major / Minor congenital malformation (CM)	Comments (Description of CMs)
(b) (6)	TAK-438 vs Lan / Capsule-UNK [bid] TAK-438 vs Lan / Capsule TAK 438_ 304 and Lan 30mg UNK [qd] Placebo / Tablet UNK [UNK] Amox / UNK 2 gm [1 gm-bid] Clarith / UNK 1000 mg [500 mg-bid] Bismuth Potassium Citrate / UNK 1200 mg [600 mg-bid]	(b) (6)	1st TM (7 weekss)	Live Birth	None	None	N/A
	Von / Tablet 20 mg [20 mg -qd]		1st TM	SAB	SAB	N/A	N/A
	TAK-438 vs Esomeprazole (Eso) / Tablet UNK [bid] Amox / UNK 2 gm [1 gm-bid] Clarith / UNK 1000 mg [500 mg-bid] Bismuth Subcitrate / UNK 1200 mg [600 mg-bid]		N/A	TAB	N/A	N/A	N/A
(See Table 2 for narrative)	TAK-438 / Tablet 20 mg [UNK] TAK438<PLACEBO>/ UNK 20 mg [UNK] received Von 20 mg		1st TM (<4 weekss)	SAB	N/A	N/A	N/A

Patient I.D. /Case #	Vonoprazan Dose (mono) / Combination regimen (list additional therapy)	Exposure Duration	Exposure Period*	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome**	Concomitant Medications (If Major / Minor congenital malformation (CM)	Comments (Description of CMs)
(b) (6)	TAK-438 / Tablet 20 mg [20 mg-qd] received Von 20 mg	(b) (6)	1st TM (1 weeks)	Live Birth	None	N/A	N/A
	TAK-438 vs Lan / Tablet 20 mg [20 mg-qd] TAK-438 vs Lan / Tablet 20 mg [20 mg-qd] received Von 20 mg		1st TM (<6 weeks)	Live Birth	None	N/A	N/A

*Gestational age or TM (TM) of exposure)

** Include major / minor congenital malformations, premature birth, low birth weight, small or large for gestational age, etc.

^Clinical Trial Cases

Source: Reviewer's Table (derived from Sponsor's "Response to IR" Table submitted on 3/11/22)

Table 7: Summary of Post-Marketing Cases with Known Pregnancy Outcome

	Patient I.D./ Case #	Vonoprazan Dose (mono treatment) / Combination regimen (list additional therapy dose as appropriate)	Exposure Duration	Exposure Period (gestational age or TM** of exposure)	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome*	Concomitant medications (If major / minor congenital malformation)	Comments (Description of congenital malformations)
1.	(b) (6)	TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	Unknown	36 weeks	Live Birth	None	N/A	N/A
2.		TAKECAB TABLETS 10mg / Tablet 10 mg [10 mg-UNK]	14 day(s)	18 weeks	Live Birth	None	N/A	N/A
3.		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	(b) (6) to Unknown	second TM (TM) (per CIOMS verbatim	Live Birth	Not Reported by reporting hospital	N/A	N/A
4.		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-qd]	(b) (6)	TM 3 (30th to 35th weeks)	Twin pregnancy-Live Birth; Weeks 36	low birth weight babies: Neonatal weight and height: (I) 2,108 g 43.6 cm; (II) 2,282 g 46.2 cm	None	N/A
5.		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	(b) (6)	second TM (15th weeks) per CIOMS verbatim	Live Birth	None	N/A	N/A
6.		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-qd]	(b) (6)	TM 3 (30th to 35th weeks)	Live Birth	None	N/A	N/A

	Patient I.D./ Case #	Vonoprazan Dose (mono treatment) / Combination regimen (list additional therapy dose as appropriate)	Exposure Duration	Exposure Period (gestational age or TM** of exposure)	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome*	Concomitant medications (If major / minor congenital malformation)	Comments (Description of congenital malformations)
7.	(b) (6)	TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	Unknown	Unknown	Live Birth	None	N/A	N/A
8.		Vonosap Pack 400 / Capsule (VONOPRAZAN FUMARATE, AMOXICILLIN, CLARITHROMYCIN) 1 dosage form [.5 dosage form-bid]	(b) (6)	TM 1	Abortion	Abortion	N/A	N/A
9.		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	Unknown	TM 3 (30th weeks or later)	Live Birth	None	N/A	N/A
10		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	Unknown	TM 3 (30th weeks or later)	Live Birth	None	N/A	N/A
11		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	Unknown	TM 3 (30th weeks or later)	Live Birth	None	N/A	N/A
12		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	(b) (6)	TM 3 (weeks 36)	Live Birth	Premature delivery (low birth weight baby, small for gestational age or infant small in early perinatal dates; hx of premature	N/A	N/A

	Patient I.D./ Case #	Vonoprazan Dose (mono treatment) / Combination regimen (list additional therapy dose as appropriate)	Exposure Duration	Exposure Period (gestational age or TM** of exposure)	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome*	Concomitant medications (If major / minor congenital malformation)	Comments (Description of congenital malformations)
						labor at weeks 29)		
13	(b) (6)	TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	(b) (6)	TM 3 (weeks 34)	Live Birth	None	N/A	N/A
14		TAKECAB TABLETS 20mg / Tablet 10 mg [10 mg-UNK]		TM 3 (weeks 33)	Live Birth	Obstructed labour	N/A	N/A
15		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		TM 1 (weeks 10)	Live Birth - twins	Premature labour-weeks 32 / delivery weeks 37; low birth weight (2124 g / 2220g);	N/A	N/A
16		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		TM 1 (weeks 7)	Live Birth	Premature rupture of membranes (weeks 34) low birth weight 2082 g.	N/A	N/A
17		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		30 weeks	Live Birth	None	N/A	N/A
18		TAKECAB TABLETS 20mg / Tablet 10 mg [10 mg-UNK]		18 weeks	Live Birth	None	N/A	N/A

	Patient I.D./ Case #	Vonoprazan Dose (mono treatment) / Combination regimen (list additional therapy dose as appropriate)	Exposure Duration	Exposure Period (gestational age or TM** of exposure)	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome*	Concomitant medications (If major / minor congenital malformation)	Comments (Description of congenital malformations)
19	(b) (6)	TAKECAB TABLETS 20mg / Tablet 10 mg [10 mg-UNK]	(b) (6)	22 weeks	Live Birth	None	N/A	N/A
20		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		12 weeks	Live Birth	None	N/A	N/A
21		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		32 weeks	Live Birth	None	N/A	N/A
22		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		34 weeks	Twin pregnancy-Live Birth; Weeks 34	Premature delivery; low birth weight; SGA/SFD	N/A	N/A
23		TAKECAB TABLETS 20mg / Tablet 10 mg [10 mg-UNK]		14 weeks	Live Birth	None	N/A	N/A
24		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		17 weeks	Live Birth	None	N/A	N/A
25		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		33 weeks	Live Birth	None	N/A	N/A
26		TAKECAB TABLETS 20mg / Tablet 10 mg [10 mg-UNK]		34 weeks	Live Birth	Premature delivery; low birth weight	N/A	N/A
27		TAKECAB TABLETS 20mg / Tablet 10 mg [10 mg-UNK]		35 weeks	Live Birth	Premature delivery; low birth weight	N/A	N/A

	Patient I.D./ Case #	Vonoprazan Dose (mono treatment) / Combination regimen (list additional therapy dose as appropriate)	Exposure Duration	Exposure Period (gestational age or TM** of exposure)	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome*	Concomitant medications (If major / minor congenital malformation)	Comments (Description of congenital malformations)
28	(b) (6)	TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	(b) (6)	31 weeks	Live Birth	None	N/A	N/A
29		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		33 weeks	Live Birth	Premature delivery; neonatal asphyxia	N/A	N/A
30		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		16 weeks	Live Birth	None	N/A	N/A
31		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		32 weeks	Twin pregnancy-Live Birth; Weeks 34	Premature delivery; asphyxia; low birth weight	N/A	N/A
32		TAKECAB TABLETS 20mg / Tablet 10 mg [10 mg-UNK]		16 weeks	Live Birth	None	N/A	N/A
33		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		17 weeks	Live Birth	Respiratory disorder; hyperbilirubinemia	N/A	N/A
34		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		22 weeks	Live Birth	None	N/A	N/A
35		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		10 weeks	Live Birth	None	N/A	N/A

	Patient I.D./ Case #	Vonoprazan Dose (mono treatment) / Combination regimen (list additional therapy dose as appropriate)	Exposure Duration	Exposure Period (gestational age or TM** of exposure)	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome*	Concomitant medications (If major / minor congenital malformation)	Comments (Description of congenital malformations)
36	(b) (6)	TAKECAB TABLETS 10mg / Tablet 10 mg [10 mg-UNK]	(b) (6)	30 weeks	Live Birth	Respiratory disorder	N/A	N/A
37		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		12 weeks	Live Birth	Foetal distress syndrome	N/A	N/A
38		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		35 weeks	Live Birth	Premature delivery; low birth weight; SGA/SFD	N/A	N/A
39		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		10 weeks	Twin pregnancy-Live Birth; Weeks 37	Low birth weight; SGA/SFD	N/A	N/A
40		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		10 weeks	Twin pregnancy-Live Birth; Weeks 37	Low birth weight; SGA/SFD	N/A	N/A
41		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		7 weeks	Live Birth	Premature delivery; low birth weight	N/A	N/A
42		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		34 weeks	Twin pregnancy-Live Birth; Weeks 34	Premature delivery; low birth weight; SGA/SFD	N/A	N/A
43		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		34 weeks	Twin pregnancy-Live Birth; Weeks 34	Premature delivery; low birth weight; SGA/SFD	N/A	N/A

	Patient I.D./ Case #	Vonoprazan Dose (mono treatment) / Combination regimen (list additional therapy dose as appropriate)	Exposure Duration	Exposure Period (gestational age or TM** of exposure)	Pregnancy Outcome (Live birth, miscarriage, termination, still birth)	Adverse Pregnancy Outcome*	Concomitant medications (If major / minor congenital malformation)	Comments (Description of congenital malformations)
44	(b) (6)	TAKECAB TABLETS 20mg / Tablet 10 mg [10 mg-UNK]	(b) (6)	31 weeks	Live Birth	Premature delivery; low birth weight	N/A	N/A
45		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		32 weeks	Twin pregnancy-Live Birth; Weeks 34	Premature delivery; asphyxia; low birth weight	N/A	N/A
46		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]		32 weeks	Twin pregnancy-Live Birth; Weeks 34	Premature delivery; asphyxia; low birth weight	N/A	N/A
47		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-qd]		22 weeks	Live Birth	None	N/A	N/A
48		TAKECAB TABLETS 20mg / Tablet 20 mg [20 mg-UNK]	Unknown	Unknown	Live Birth	Unknown	N/A	N/A

*Include major / minor congenital malformations, premature birth, low birth weight, small or large for gestational age, etc.

**TM=trimester

Source: Reviewer's Table (derived from Sponsor's "Response to IR" Table submitted on 3/11/22)

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/

JANE E LIEDTKA
03/24/2022 03:05:07 PM

TAMARA N JOHNSON
03/24/2022 03:43:17 PM

LYNNE P YAO
03/25/2022 06:45:54 AM

MEMORANDUM

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

DATE: March 11, 2022

TO:
Leah Rosenfeld – Pharmacology Toxicology Reviewer
Terry Miller – Pharmacology Toxicology TL
Eva Zuffova, DAI - RPM

THROUGH:
Juli Tomaino, MD
Deputy Director, Division of Gastroenterology (DG)

FROM:
Laura Finkelstein, MD, MPS
Clinical Reviewer, DG

Joette Meyer, PharmD
Clinical Team Leader, DG

Dinesh Gautam, Ph.D.
Pharmacologist, PT-II

Jackye Peretz, Ph.D.
Lead Toxicologist, PT-II

Sushanta Chakder, Ph.D.
Supervisory Pharmacologist, PT-II

SUBJECT: Labeling consult request from Division of Anti-Infectives (DAI) regarding the Applicants request for a new Established Pharmacologic Class (EPC) for vonoprazan.

Addendum: Response to Applicant Rebuttal

APPLICATION/DRUG: NDA 215152/215153

Application Type	**Number**	**Name of Drug**
NDA	215152	vonoprazan tablets 20 mg/amoxicillin capsules 500 mg, (b) (4) clarithromycin tablets, 500 mg, (b) (4)
NDA	215153	Vonoprazan/Amoxicillin
Sponsor	Phathom Pharmaceuticals	
Proposed indication	Treatment of *Helicobacter pylori*	

Background:

Both vonoprazan and the currently approved proton pump inhibitors (PPIs) inhibit the gastric proton pump to block acid release. However, the mechanism by which vonoprazan inhibits the proton pump differs from the currently approved PPIs. PPIs require activation by gastric acid and bind covalently to the gastric proton pump, with permanent deactivation of the proton pump. In contrast, vonoprazan reversibly and competitively binds the gastric proton pump without requiring gastric acid activation. The Division of Gastroenterology recommended that vonoprazan be assigned the EPC of "potassium competitive proton pump inhibitor" to highlight the relationship to the approved PPIs as well as distinguishing its differences. This recommendation was communicated to the Applicant on February 24, 2022. Please refer to the consult review submitted by DG on January 26, 2022 for additional details.

On March 2, 2022, the Applicant submitted a rebuttal response to the recommendation, noting that (1) the term [PCAB] is already well established in the scientific and medical community in multiple fields and (2) it more clearly distinguishes the two classes (PCABs and PPIs) from a scientific and clinical perspective. They further note that regulatory authorities in several countries, including the country of initial approval (Japan), refer to vonoprazan as a PCAB and that professional organizations have included this term in their updated clinical guidelines.[1] DAI requested additional input from DG regarding the Applicant's rebuttal.

DG's Recommendation:

Upon review of the Applicant's rebuttal, DG continues to recommend "potassium-competitive proton pump inhibitor" as the EPC for vonoprazan but will not oppose the Applicant's requested EPC of "potassium-competitive acid blocker" (PCAB), provided the labeling in section 12.1 includes reference to vonoprazan as a PPI. See proposal below.

Summary Rationale

As discussed in the DG consult review, describing vonoprazan as a PCAB is a scientifically valid description of how vonoprazan inhibits the proton pump, with resulting reduction of acid secretion. Even so, the site of pharmacologic activity of vonoprazan that is shared with the approved PPIs (i.e., at the proton pump) is not captured by the description of vonoprazan as a PCAB. As a result, the EPC of PCAB is not a complete, clinically meaningful description of vonoprazan (refer to MaPP 7400.13). Both vonoprazan and PPIs share a common site of pharmacologic activity and subsequent therapeutic effect (i.e., proton pump inhibition). However, vonoprazan should be distinguished from the approved PPIs without fully separating the two classes of compounds. Vonoprazan is not a benzimidazole compound, does not require an acid medium for activation, and inhibits the activity of the proton pump faster, more potently, and for a longer duration than the approved PPIs. To include the commonalities in the EPC designation without implying that they are identical in clinical action, DG recommended "potassium competitive proton pump inhibitor" as the EPC for vonoprazan.

[1] Iwakiri, K, Y Fujiwara, N Manabe, E Ihara, S Kuribayashi, J Akiyama, T Kondo, H Yamashita, N Ishimura, Y Kitasako, K Iijima, T Koike, N Omura, T Nomura, O Kawamura, S Ohara, S Ozawa, Y Kinoshita, S Mochida, N Enomoto, T Shimosegawa and K Koike (2022). "Evidence-Based Clinical Practice Guidelines for Gastroesophageal Reflux Disease 2021." J Gastroenterol.

The term PCAB is used frequently in scientific literature and appears to be understood by the medical community. However, use of the term is found predominantly in articles that reference vonoprazan specifically and it is possible that the use of the term is driven by the Applicant's use of the term, rather than general acceptance, given that other authors use different terminology to describe the group of drugs (e.g., "new generation PPIs").[2]

The Applicant's rebuttal position is partly based on clinical experience with vonoprazan in other countries where the term PCAB is in use. Of note, the PMDA approved label in Japan refers to vonoprazan as both a PCAB and PPI in the title header (see Appendix). Other regulatory authorities describe drugs in this class as "reversible acid pump antagonists". Additionally, the WHO Collaborating Centre for Drug Statistics Methodology, a central body responsible for coordinating the use of the Anatomical Therapeutic Chemical Classification (ATC) methodology for exchanging and comparing data on drug use,[3] has assigned vonoprazan the ATC code prefix (A02BC) for PPIs.

As previously noted, regardless of which term is used as the EPC, there can be synonyms associated with the EPC term in the Medical Reference Terminology database and PCAB would still be a 'child' of the PPIs.

Vonoprazan Labeling Recommendation

DG recommends that the Prescribing Information (PI) for NDAs 215152/215153 include language in Section 12.1 that includes reference to vonoprazan as a PPI. Suggested language with annotations is included below with underline (proposed additions) and strikethrough (proposed deletions). The wording is similar to the wording in Section 12.1 of multiple approved PPIs. Other edits are suggested for this section based upon the submitted nonclinical information. However, these edits are suggestions, and DG defers to the DAI nonclinical team for the final decision on the wording.

(b) (4)

12 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

LAURA H FINKELSTEIN
03/11/2022 12:09:58 PM

DINESH C GAUTAM
03/11/2022 12:30:33 PM

JACKYE R PERETZ
03/11/2022 01:06:26 PM

SUSHANTA K CHAKDER
03/11/2022 01:33:53 PM

JOETTE M MEYER
03/11/2022 01:59:43 PM

JULI A TOMAINO
03/11/2022 02:02:37 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:	March 9, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215152 and NDA 215153
Product Name and Strength:	vonoprazan; amoxicillin; clarithromycin vonoprazan tablets, 20 mg; amoxicillin capsules, 500 mg; and clarithromycin tablets, 500 mg vonoprazan; amoxicillin vonoprazan tablets, 20 mg and amoxicillin capsules, 500 mg
Applicant/Sponsor Name:	Phathom Pharmaceuticals, Inc.
OSE RCM #:	2021-1750-1 and 2021-1752-1
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 25, 2022 for vonoprazan; amoxicillin; and clarithromycin triple pak and for vonoprazan; amoxicillin dual pak. The Division of Anti-Infectives (DAI) requested that we review the revised container labels and carton labeling for vonoprazan; amoxicillin; and clarithromycin triple pak and for vonoprazan; amoxicillin dual pak (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]

[a] Birkemeier D. Label and Labeling Review for (b) (4) Triple Pak (vonoprazan; amoxicillin; and clarithromycin) and (b) (4) Dual Pak (vonoprazan; amoxicillin) (NDA 215152 and NDA 215153). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 DEC 9. RCM No.: 2021-1750 and 2021-1752.

2 CONCLUSION

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

Appears this way on original

12 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

DAMON A BIRKEMEIER
03/09/2022 05:23:21 PM

VALERIE S VAUGHAN
03/09/2022 05:33:30 PM

MEMORANDUM

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

DATE: February 18, 2022

TO:
Mayurika Ghosh – Clinical Reviewer
Thomas Smith – Clinical TL
Eva Zuffova, DAI - RPM

THROUGH:
Joette Meyer – Clinical TL – Division of Gastroenterology
Juli Tomaino – Deputy Director - Division of Gastroenterology

FROM:
Laura Finkelstein – Clinical Reviewer – Division of Gastroenterology

SUBJECT:
Safety consult request from Division of Anti-Infectives (DAI) regarding the possible increased risk of fractures with vonoprazan.

APPLICATION/DRUG: NDA 215152/215153

Application Type	**Number**	**Name of Drug**
NDA	215152	vonoprazan tablets 20 mg/amoxicillin capsules 500 mg, (b) (4) clarithromycin tablets, 500 mg, (b) (4)
NDA	215153	Vonoprazan/Amoxicillin
Sponsor	Phathom Pharmaceuticals	
Proposed indication	Treatment of *Helicobacter pylori*	

Regulatory History

Vonoprazan is currently under review by DAI under NDAs 215152 and 215153 co-packaged with amoxicillin and/or clarithromycin for treatment of *Helicobacter pylori* (referencing INDs 143190 and 144399). (b) (4) Vonoprazan has received regulatory approval in Japan and other countries in Asia and Latin America for indications of EE healing and maintenance, gastric ulcer/duodenal ulcer healing, and for the prevention of recurrence of a gastric or duodenal ulcer during nonsteroidal anti-inflammatory drugs or aspirin administration.

On January 11, 2022, DAI consulted the Division of Gastroenterology requesting:

A brief summary of short term (dosing for 14 days) risks of potassium-competitive acid blockers and PPIs, including potential bone fracture, which can be used to inform our NDA review and labeling.

Following a teleconference with Mayurika Ghosh and Thomas Smith on January 13, 2022, the

consult question from DAI to DG was modified to the following:

Please comment on short-term risks that have been identified with PPIs or drugs with a similar mechanism of action. Do these risks appear to be increased with concomitant use of amoxicillin and clarithromycin?

As further noted in the original consult request:

> Current PPIs are labeled with a Warning and Precaution of bone fracture associated with long-term PPI use. In the NDA submissions for treatment of *H pylori* (HP) infection, there were 2 cases (serious adverse events) of bone fracture noted in the pivotal phase 3 trial HP-301 with vonoprazan dual therapy and triple therapy (1 each). The Applicant also summarized the risk of bone fracture in short term (2-8 weeks) and long-term studies (>8 weeks) of vonoprazan use in non-HP indications. In the placebo-controlled short-term studies pool, the incidence of TEAEs associated with bone fracture was 0.4% in the overall vonoprazan group compared with no reports in the placebo group.
>
> In the PPI-controlled short-term studies pool, the overall vonoprazan and PPI groups were comparable with respect to the incidence of TEAEs associated with bone fracture (0.2% in each group). In the long-term studies pool, TEAEs associated with bone fracture were experienced in 1.7% of the overall vonoprazan group.
> In the lansoprazole-controlled long-term studies pool, the overall vonoprazan and lansoprazole groups were comparable with respect to the incidence of TEAEs associated with bone fracture (2.0% and 1.4%, respectively). Spinal compression fracture was experienced in 14 (0.8%) subjects in the overall vonoprazan group compared with no reports in the lansoprazole group.

Summary of Risks with Proton Pump Inhibitors

Bone Fracture Risk

Proton pump inhibitors (PPIs) are a class of drugs which act to suppress acid secretion through irreversible inactivation of the gastric H+/K+ ATPase ("proton pump") to treat gastric and duodenal ulcers, gastroesophageal reflux disease and other excessive gastrointestinal acid secretory disorders. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Vonoprazan is the first to seek regulatory approval in a new class of drugs that acts to inhibit gastric acid release through potassium-competitive inhibition of the gastric H+/K+ ATPase. These drugs are known in the scientific literature as potassium-competitive acid blockers (PCABs).

Some biologic evidence suggests that PPIs may influence bone mineral homeostasis and therefore affect bone health, which may increase the risk of fracture. Multiple mechanisms have been proposed to explain this effect, including effects of high gastric pH on micronutrient absorption (Briganti 2021), increased bone resorption through the action of elevated serum gastrin and parathyroid hormone (PTH), and direct local interaction between PPI drugs and receptors and/or enzymes found in bone (Ankar 2022; Staines 2021; Qin 2012). However, the process remains unproven and is likely multifactorial (Briganti 2021).

Several epidemiologic studies have suggested an increased risk of fractures of the hip, wrist, and spine with PPI use, with the greatest risk among older individuals who have used PPIs for at least one year or who took high doses of PPIs.[1] After reviewing these epidemiologic studies, in 2010 FDA added safety information to the product labels for prescription PPIs stating that there was a possible increased risk of osteoporosis-related fracture with the use of these medications with high dose, long-

[1] Medical Officer's FDAAA Safety Labeling Review: Tracked Safety Issue #63 -- Proton Pump Inhibitors and Hip Fracture by Tamara Johnson, September 21, 2010, Reference ID: 2840836. Retrievable at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af801f5fc6&_afrRedirect=999744264649974

term therapy.[2] The non-prescription PPIs were excluded from the Safety Labeling Change, as they were only intended to be used for 14 days up to 3 times yearly.[3] More recently in 2015, an assessment of the relationship between PPI use and fractures in children and young adults failed to demonstrate an association that would support a change in labeling.[4]

All prescription single-ingredient PPI product labels currently have language about bone fractures. Approved class labeling in the Prescribing Information for Prilosec (omeprazole magnesium), as a representative PPI with extensive use, is used for illustration:[5]

> ***5 WARNINGS AND PRECAUTIONS***
>
> ***5.4 Bone Fracture***
>
> *Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the conditions being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines*
>
> ***6 ADVERSE REACTIONS***
> ***6.2 Postmarketing Experience***
>
> *Musculoskeletal System Disorders: bone fracture*

It should be noted that neither a review of the medical literature nor the reviews conducted previously by FDA demonstrate an association between short-term use of PPIs and increased risk of fracture. Bone fracture was not identified as a safety-signal in the clinical trials of PPIs for any of the approved indications. Most clinical trials were 8 weeks or less; controlled studies did not extend beyond 12 months for the maintenance indication(s). Bone fracture as a safety signal was identified in epidemiologic studies with large numbers of patients receiving various doses, including high doses, over prolonged periods of time.

Other Identified Risks

Long-Term Risks

Other than bone fracture, the PPI drug class is labeled for the several serious or otherwise clinically significant adverse reactions identified during investigations and post-marketing surveillance. The following risks of long-term use of PPIs were added to the Warnings and Precautions section of the label as part of class safety labeling changes (SLCs), after identification during post-marketing analysis of epidemiologic data:[5]

> **5.7 Cyanocobalamin (Vitamin B-12) Deficiency**
>
> Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of

---

[2] FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. 5-25-2010. Retrievable at: https://www fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-possible-increased-risk-fractures-hip-wrist-and-spine-use-proton-pump

[3] Memorandum: Long-term Use of Proton Pump Inhibitors and Risk of Fracture by Lolita Lopez, April 6, 2010 (updated September 3, 2010), Reference ID: 2858577. Retrievable at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af801ff2d9

[4] Epidemiology: Literature Review by Gabriella Anic, August 13, 2015, Reference ID: 3806172. Retrievable at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803a6aca&_afrRedirect=989870458842028

[5] Prescribing Information, PRILOSEC (omeprazole magnesium), updated November 2020, retrieved on February 15, 2022 from: http://fdalabel.fda.gov/fdalabel/services/spl/set-ids/b6761f84-53ac-4745-a8c8-1e5427d7e179/spl-doc?hl=Prilosec#section-5

cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with PRILOSEC.

5.8 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically *[see Adverse Reactions (6.3)]*.

5.12 Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Short and/or Long-Term Risks

Analysis of post-marketing epidemiologic data also led to the following class SLCs for risks that were **not specifically related to long-term use**[6]:

5.2 Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia).Discontinue PRILOSEC and evaluate patients with suspected acute TIN [see Contraindications (4)].

5.3 *Clostridium difficile*-Associated Diarrhea

Published observational studies suggest that PPI therapy like PRILOSEC may be associated with an increased risk of *Clostridium difficile*-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve *[see Adverse Reactions (6.2)]*.

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with PRILOSEC, refer to *Warnings and Precautions* sections of the corresponding prescribing information.

5.5 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including omeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

[6] PI, Prilosec 2020

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving PRILOSEC, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

(b) (4)

Hormonal and Endocrine Effects

See Section 12.2 of the prescribing information for the individual PPIs[8] for details of other effects on hormones and endocrine function that have been investigated with short term use.

Risks of Antibiotics with PPIs

Regarding risks specific to the use of PPIs with antibiotics, the following information was taken from the currently approved PI for Prilosec (omeprazole magnesium):

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
In clinical trials using either dual therapy with omeprazole magnesium delayed-release capsules and clarithromycin, or triple therapy with omeprazole magnesium delayed-release capsules, clarithromycin, and amoxicillin, no adverse reactions unique to these drug combinations were observed. Adverse reactions observed were limited to those previously reported with omeprazole, clarithromycin, or amoxicillin alone.

Summary of Risks with Vonoprazan

The Applicant provided a summary of adverse events of special interest by organ system or syndrome in DAI's NDAs which included events associated with *C. difficile*-associated diarrhea, bone fracture, and severe cutaneous adverse reactions.[9]

We reviewed submissions to (b) (4) published information from foreign regulation of vonaprazan, and publicly available foreign post-marketing safety information.

Bone Fracture Risk

[7] (b) (4)

[8] FDALabel Query: http://fdalabel.fda.gov/fdalabel/ui/search/spl-summaries/criteria/100442
[9] Integrated Summary of Safety, NDA 215152, Retrievable at: \\CDSESUB1\evsprod\nda215152\0002\m2\27-clin-sum\summary-clin-safety.pdf

There is limited information available regarding the relationship of vonoprazan or other PCABs and fracture risk. The Applicant has identified bone fracture as an "important potential risk" addressed in the Core Risk Management Plan of the development program for vonoprazan.

Foreign Regulation

Vonoprazan is approved for marketing outside of the US, in Asia and South America. The approved label for vonoprazan (see Appendix II), marketed in Asia as Takecab (Japan) and as Vocinti (Malaysia / Korea and Thailand) (see Appendix I), carries a precaution for bone fractures based on the experience with PPIs. We refer you to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) marketing review for details of their assessment of safety (PMDA 2014).

Foreign Post-Marketing

Clinical Trials

A randomized open-label phase 4 study (i.e., VISION, Vonoprazan-4003), mandated by the PMDA to assess the long-term safety of vonoprazan for maintenance treatment of erosive esophagitis in subjects is ongoing, with 1174 subjects participating to date (Haruma 2021; Uemera 2018). The interim analysis of this study has not revealed an increased risk of fractures (Haruma 2021; USNLM 2021). (b) (4) a single case of spinal compression fracture was reported (p. 22).[10]

Other Identified Risks

As noted above, *C. difficile*-associated diarrhea, and severe cutaneous adverse reactions were identified by the Applicant as potential risks with vonoprazan. We defer to the DAI for review of the NDA 215152/215153 data.

Summary: Risks of PPIs and Vonoprazan

- PPIs are associated with increased risk of osteoporosis-related fracture, particularly with high-dose, long-term use (i.e., greater than 1 year duration). Evidence does not support an association between short-term use of PPIs and fracture risk.

- Because PPIs and PCABs cause prolonged acid suppression through inhibition of the gastric proton pump and elevate serum gastrin, it might be expected that vonoprazan and the PPIs would have similar effect on micronutrient absorption and gastrin/PTH-mediated bone homeostasis. In contrast, given differences in structure and the in the nature of the interaction with the proton-pump between PCABs and PPIs, it is unclear whether vonoprazan would interact with vATPases or phosphatases in a similar manner as that proposed for PPIs.

- As noted above, potential short-term risks of PPIs include TIN, CDAD, SLE/CLE, and (b) (4). Of particular note, although the risk of *C. difficile* infection is increased with the use of antimicrobials, a signal of excess risk from the use of PPIs and antibiotics in combination has not been identified. Further, given that acid suppression has been implicated as the mechanism for increased CDAD with PPI use, it would be reasonable to expect that vonoprazan might have similar impact on CDAD risk.

10 (b) (4)

FDA References:

(b) (4)

Epidemiology: Literature Review by Gabriella Anic, August 13, 2015, Reference ID: 3806172. Retrievable at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803a6aca&_afrRedirect=98987045884202 8

FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. 5-25-2010. Retrievable at: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-possible-increased-risk-fractures-hip-wrist-and-spine-use-proton-pump

Integrated Summary of Safety, NDA 215152, Retrievable at: \\CDSESUB1\evsprod\nda215152\0002\m2\27-clin-sum\summary-clin-safety.pdf

Medical Officer's FDAAA Safety Labeling Review: Tracked Safety Issue #63 -- Proton Pump Inhibitors and Hip Fracture by Tamara Johnson, September 21, 2010, Reference ID: 2840836. Retrievable at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af801f5fc6&_afrRedirect=99974426464997 4

Memorandum: Long-term Use of Proton Pump Inhibitors and Risk of Fracture by Lolita Lopez, April 6, 2010 (updated September 3, 2010), Reference ID: 2858577. Retrievable at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af801ff2d9

Prescribing Information, PRILOSEC (omeprazole magnesium), updated November 2020, retrieved on February 15, 2022 from: http://fdalabel.fda.gov/fdalabel/services/spl/set-ids/b6761f84-53ac-4745-a8c8-1e5427d7e179/spl-doc?hl=Prilosec#section-5

(b) (4)

Literature References:

Ankar A, Kumar A. Vitamin B12 Deficiency. [Updated 2021 Jun 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441923/

Briganti, SI, AM Naciu, G Tabacco, R Cesareo, N Napoli, P Trimboli, M Castellana, S Manfrini and A Palermo (2021). "Proton Pump Inhibitors and Fractures in Adults: A Critical Appraisal and Review of the Literature." Int J Endocrinol 2021: 8902367.

Haruma, K, Y Kinoshita, T Yao, R Kushima, J Akiyama, T Kanoo, K Miyata (2021). "3-Year Interim Analysis Results of Vision Trial: A Randomized, Open-Label Study to Evaluate the Long-Term Safety of Vonoprazan as Maintenance Treatment in Patients with Erosive Esophagitis". Digestive Diseases Week, American College of Gastroenterology.

PMDA (2014). Review Report: Vonoprazan Fumarate. Tokyo, Japan, Evaluation and Licensing

Qin, A, TS Cheng, NJ Pavlos, Z Lin, KR Dai and MH Zheng (2012). "V-Atpases in Osteoclasts: Structure, Function and Potential Inhibitors of Bone Resorption." The International Journal of Biochemistry & Cell Biology 44(9): 1422-1435.

Staines, KA, K Myers, K Little, SH Ralston and C Farquharson (2021). "Proton Pump Inhibitors Inhibit Phospho1 Activity and Matrix Mineralisation in Vitro." Calcif Tissue Int 109(6): 696-705.

Uemura, N, Y Kinoshita, K Haruma, T Yao, R Kushima and T Kanoo (2018). "Rationale and Design of the Vision Study: A Randomized, Open-Label Study to Evaluate the Long-Term Safety of Vonoprazan as Maintenance Treatment in Patients with Erosive Esophagitis." Clin Exp Gastroenterol 11: 51-56.

United States National Library of Medicine, Clinical Trials.gov, Special Drug Use Surveillance of Vonoprazan for "Maintenance Therapy of Reflux Esophagitis: Long-term Use", Identifier NCT03214081, retrievable at: https://clinicaltrials.gov/ct2/show/NCT03214081?term=vonoprazan&cntry=JP&draw=2&rank=4

Zanaty, MI, A Abdel-Moneim, Y Kitani, T Sekiguchi and N Suzuki (2021). "Effect of Omeprazole on Osteoblasts and Osteoclasts in Vivo and in the in Vitro Model Using Fish Scales." Biochemistry (Mosc) 86(10): 1192-1200.

Appendices

I. Links to International Drug Labels

- Thailand: http://ndi.fda.moph.go.th/uploads/drug_detail_corporation/doc/word/1163/59617143799c78416f40a1fd7d1442e5-a1.pdf

- Malaysia: https://www.mims.com/malaysia/drug/info/vocinti?type=full

II. Product Labeling, vonoprazan fumarate, Japan (translated for FDA) - Attached

11 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

LAURA H FINKELSTEIN
02/18/2022 06:50:48 AM

JOETTE M MEYER
02/18/2022 08:19:58 AM

JULI A TOMAINO
02/18/2022 08:21:08 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215152 / 215153
Submission Number	002 (New NDA)
Submission Date	9/3/2021
Date Consult Received	12/7/2021
Drug Name	Vonoprazan/Amoxicillin/Clarithromycin
Indication	Treatment of Helicobacter pylori (H pylori) infection
Therapeutic Dose	20 mg BID
Clinical Division	DAI
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 12/7/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 11/02/2020 in DARRTS (link);
- Study TAK-438_111 Clinical Study Report Addendum – TQT (SN0002; link)
- Study TAK-438_111 Clinical Study Report Amendment 1.0 (SN0002; link)
- Investigator's brochure, V 11 (SN0002; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0002; link).

1 SUMMARY

In this thorough QT study of vonoprazan, no significant effect on QTcF prolongation was detected.

Study TAK-438_111 was a randomized, 4-period, 4-sequence, double blind (moxifloxacin open label), crossover design study with placebo and positive control. The highest dose evaluated was single dose of 120 mg, which covers the worst-case exposure scenario (i.e., severe renal and hepatic impairment increases vonoprazan Cmax by approximately 80%) as described in Previous IRT review.

Data were analyzed using by-time analysis as the primary analysis, which did not suggest that vonoprazan is associated with QTc interval prolongation (refer to section 4.3) – see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for overall results. Findings of this analysis are further supported by the available nonclinical data (section 3.1.2), exposure-response analysis (section 4.5) and categorical analysis (section 4.4).

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Time (h)	ΔΔQTcF (msec)	90% CI (msec)
QTc	Vonoprazan 40 mg	8	2.2	(0.4 to 4.1)
QTc	Vonoprazan 120 mg	8	3.9	(2.0 to 5.7)

For further details of the FDA analysis, please see section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable

1.2 COMMENTS TO THE REVIEW DIVISION

Vonoprazan increases clarithromycin Cmax by about 1.6-fold which is not substantially higher than the increase in clarithromycin Cmax with saquinavir (1.4-fold). Saquinavir is an anti-HIV medication that prolongs the QTc interval and can be **used with caution** during clarithromycin treatment (section 7 of claritromycin product labeling). Therefore, it seems reasonable that the QT prolongation warnings (section 5.2) for clarithromycin as a component of (b) (4) TRIPLE PAK is the same as in Section 5.2 of claritromycin product labeling

2 RECOMMENDATIONS

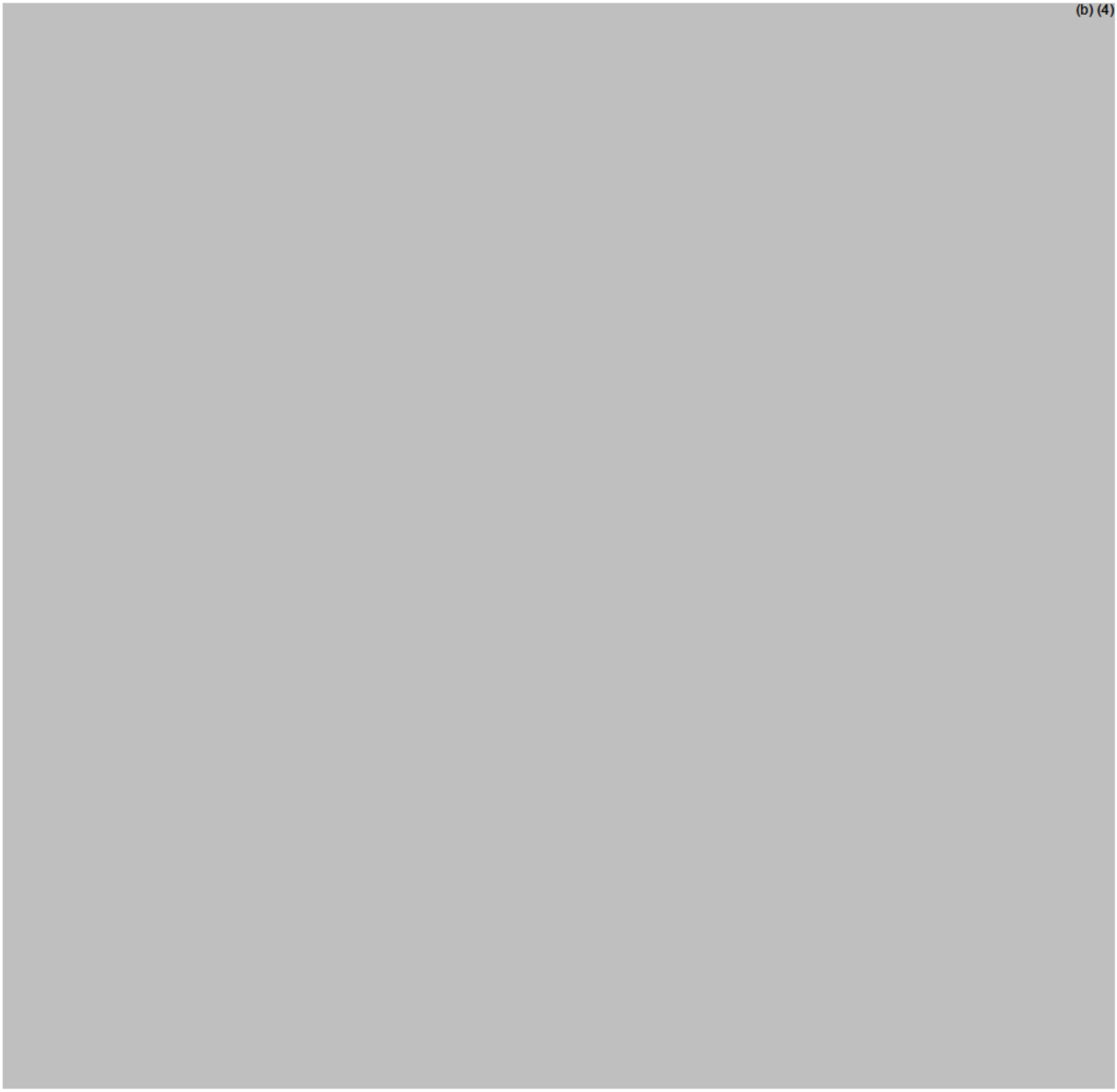
2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

We do not have edits to the label submitted to SDN 002. The decription in section 5.2 is similar to clarithromycin product labeling (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9aaffb41-408c-4372-8fd5-1d649450c0e9).

(b) (4)



3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

The Sponsor's QT assessment strategy was reviewed previously (link). In brief, the sponsor conducted a thorough QT study aimed at determining the QTc effect of vonoprazan (TAK-438) at both a therapeutic dose (40 mg) and a supra-therapeutic dose (120 mg). The thorough QT study randomized 64 healthy subjects in a 1:1:1:1 ratio to one of 4 treatment sequences (ABDC, BCAD, CDBA, and DACB; where A=TAK-438 120 mg, B=TAK-438 40 mg, C=placebo, and D=moxifloxacin 400 mg) to receive a single dose of an assigned treatment per period in 4 treatment periods separated by 4

days. Continuous (24 hour) ECG recordings were obtained at day -1 (Baseline day), day 1 (Period 1), day 6 (period 2), day 11 (period 3) and day 16 (period 4). On each ECG day, 10-second triplicate ECGs were extracted at PK sample collection time points i.e., at predose (0 h), and at 0.5, 1, 1.5, 2, 3, 4, 5, 5.5, 6, 8, 12, 16, and 24 hours after dose. The primary endpoint was the mean difference in the post-dose, time-matched, Baseline-adjusted QTcF between vonoprazan and placebo and between moxifloxacin and placebo (ddQTcF). The by-time point analysis (IUT) was used as the primary statistical analysis strategy while concentration-QTc (C-QTc) modeling was the secondary analysis strategy. For the by-time point analysis, the dependent variable was a baseline-adjusted QTcF (dQTcF) which was obtained by subtracting day -1 time matched QTcF from post-treatment QTcF in the 4 treatment periods. The dQTcF was described by a repeated measure mixed effects model in which time, sequence, period, treatment (not combining TAK-438 doses), baseline QTcF (mean of day – 1 QTcF) and time by treatment interaction were fixed effects covariates while subjects nested within sequence were random effects. For concentration-QT analysis, the dependent variable, ddQTcF, was described by a linear mixed effects model with intercept and slope for vonoprazan concentrations as fixed effects, subject level random effects for intercept and slope, and residual random error.

In the previous review, the FDA recommended using the predose (0 h) QTcF data in each period as the baseline for derivation of dQTcF and ddQTcF in the respective periods instead of using the time matched day -1 QTcF for such derivation. The FDA also recommended performing multiplicity adjustments in the assay sensitivity assessments.

In the current submission, the Applicant has revised the analyses to use the predose (0 h) adjusted QTcF (dQTcF) and the placebo corrected dQTcF (ddQTcF) as the dependent variables for the by-time point and the C-QTc analyses respectively.

3.1.2 Nonclinical Safety Pharmacology Assessments

The sponsor's non-clinical evaluation of the proarrhythmic potential of vonoprazan is summarized in the previous IRT review (link).

3.1.3 By-Time Analysis

In the sponsor's by-time analysis, TAK-438 excluded the 10 msec threshold at both dose levels tested for ΔΔQTcF.

Reviewer's comment: *The reviewers' assessment shows results similar to the sponsor's results for ΔΔQTcF. Please see Section 4.3 for more details.*

3.1.3.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *The reviewers' assessment shows results similar to the sponsor's results. Please see Section 4.3.1.1 for more details.*

The sponsor did not perform moxifloxacin exposure-response for assay sensitivity.

Reviewer's comment: *Results of the reviewer's moxifloxacin exposure versus QTcF analysis are presented in section 4.5.1.1.*

3.1.3.1.1 QT Bias Assessment

Not applicable.

3.1.4 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *The reviewers' assessment shows results similar to the sponsor's results. Please see Section 4.4 for more details.*

3.1.5 Exposure-Response Analysis

The sponsor performed linear mixed modeling of baseline-adjusted, placebo-corrected QTcF (ddQTcF) as the dependent variable and vonoprazan concentration as the only independent predictor. The model was parameterized as presented in Equation 1. Although the hysteresis plots indicated a 6 hour delay between mean Tmax and largest mean ddQTcF, the largest mean ddQTcF did not exceed 5 msec at ≥ 3 timepoints and therefore the sponsor did not account for hysteresis in the C-QTcF analysis.

$$\Delta\Delta QTcF_{kt} = \mu + \eta_{\mu} + (\theta + \eta_{\theta}) \times Conc_{kt} + \varepsilon$$

Equation 1. Linear mixed effect model for double delta. μ = Intercept, θ = slope, η = subject level random effect, ε = residual error, k subject, t timepoint.

For the primary endpoint ddQTcF, the model-based estimates of ddQTcF at mean TAK-438 plasma Cmax after administration of TAK-438 at 40 and 120 mg (45.66 ng/mL and 212.97 ng/mL, respectively) were -0.0950 msec (90% CI: -0.4964 msec; 0.3064 msec) and -0.4430 msec (90%CI: -2.3149 msec; 1.4289 msec), respectively, and the slope was negative and not statistically significant, indicating no effect of TAK-438 plasma concentrations on ddQTcF.

Reviewer's comment: *The sponsor used a linear mixed effects model that is acceptable for assessment of QT effects of drugs in crossover study designs. However, the sponsor's results differ from the reviewer's results presented in section 4.5.1. The reviewer's C-QTc analysis finds that the predicted ddQTcF at mean Cmaxes after 40 mg and 120 mg single doses are 0.4(- 0.1 – 0.8) and -0.7 (-1.8 – 0.5) respectively.*

3.1.6 Safety Analysis

The sponsor included all 64 subjects in the safety analysis dataset as all received at least 1 dose of the study drug. There were no deaths or serious adverse events. One subject in sequence DACB had a tonsilitis (moderate severity) 2 days after receiving 120 mg of vonoprazam. This TEAE led to treatment discontinuation. A summary of other TEAEs is presented below.

Table 12.c TEAEs Reported in ≥2 Subjects During the Study

SOC Preferred Term (a,b)	Number of Subjects (%) Placebo N=63	TAK-438 40 mg N=63	TAK-438 120 mg N=64	Moxifloxacin 400 mg N=64	Total Across Treatments N=64
Any TEAE	4 (6.3)	11 (17.5)	12 (18.8)	12 (18.8)	31 (48.4)
Gastrointestinal disorders	2 (3.2)	3 (4.8)	7 (10.9)	6 (9.4)	15 (23.4)
Nausea	0	1 (1.6)	5 (7.8)	2 (3.1)	8 (12.5)
Abdominal pain	1 (1.6)	1 (1.6)	1 (1.6)	2 (3.1)	4 (6.3)
Diarrhoea	2 (3.2)	1 (1.6)	1 (1.6)	0	3 (4.7)
Vomiting	0	0	1 (1.6)	1 (1.6)	2 (3.1)
Nervous system disorders	1 (1.6)	6 (9.5)	6 (9.4)	5 (7.8)	15 (23.4)
Headache	1 (1.6)	6 (9.5)	5 (7.8)	3 (4.7)	12 (18.8)
Respiratory, thoracic and mediastinal disorders	0	1 (1.6)	1 (1.6)	0	2 (3.1)
Oropharyngeal pain	0	1 (1.6)	1 (1.6)	0	2 (3.1)
Vascular disorders	0	0	1 (1.6)	2 (3.1)	3 (4.7)
Hot flush	0	0	1 (1.6)	2 (3.1)	3 (4.7)

Source: Table 15.3.1.2.1.
(a) Adverse events were coded using MedDRA version 15.0.
(b) If a subject experienced >1 TEAE that coded to the same preferred term, the subject was counted only once for that PT. If a subject experienced >1 TEAE within a SOC, the subject was counted only once for that SOC.

Source Sponsor's Clinical Study Report TAK-438_111, Amendment 1.0, page 75 of 83

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., unexplained syncope, seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and a compound symmetric covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of **ΔΔ**QTcF for different treatment groups. The maximum **ΔΔ**QTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

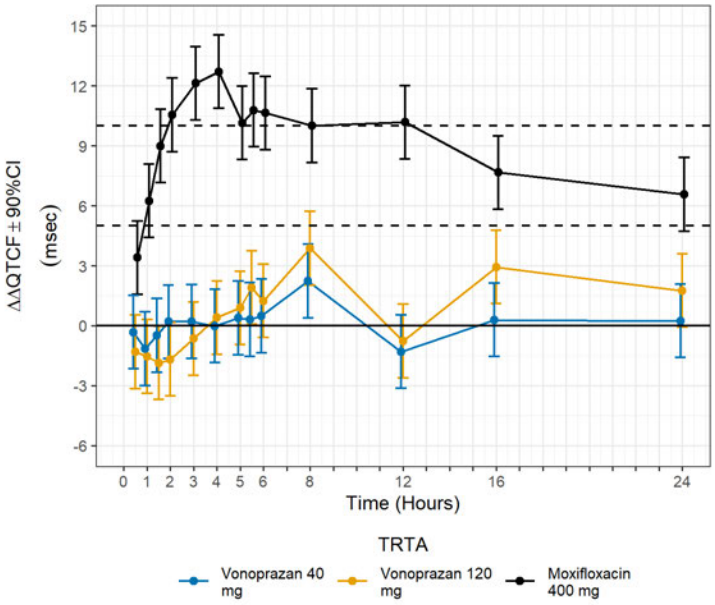


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	N_{act} / N_{pbo}	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
Vonoprazan 40 mg	62 / 62	8.0	2.2	(0.4 to 4.1)
Vonoprazan 120 mg	63 / 62	8.0	3.9	(2.0 to 5.7)

4.3.1.1 Assay Sensitivity

The time-course of changes in **ΔΔ**QTcF after receiving moxifloxacin in shown in Figure 1. The result suggests the maximum expected time-profile having a mean effect of above 5 msec after Bonferroni adjustment for 4 time points (Table 3).

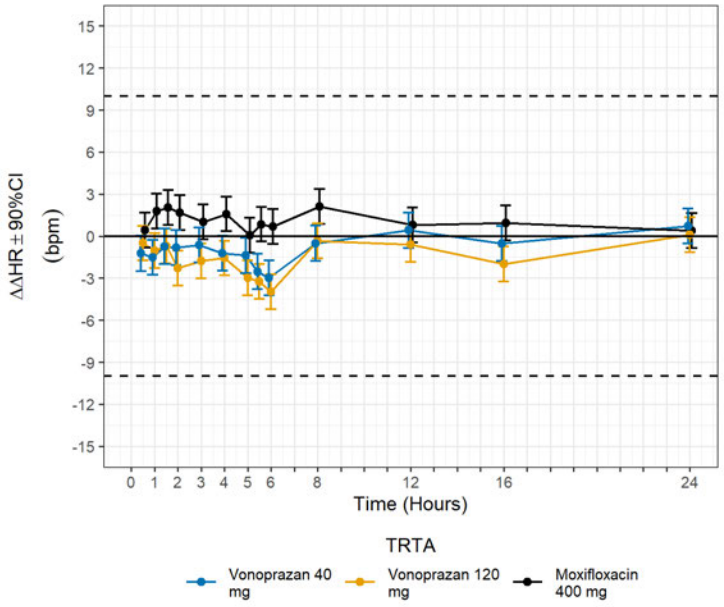
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	63 / 62	4.0	12.7	(10.9 to 14.5)	(10.2 to 15.2)

4.3.2 HR

Figure 2 displays the time profile of **ΔΔ**HR for different treatment groups.

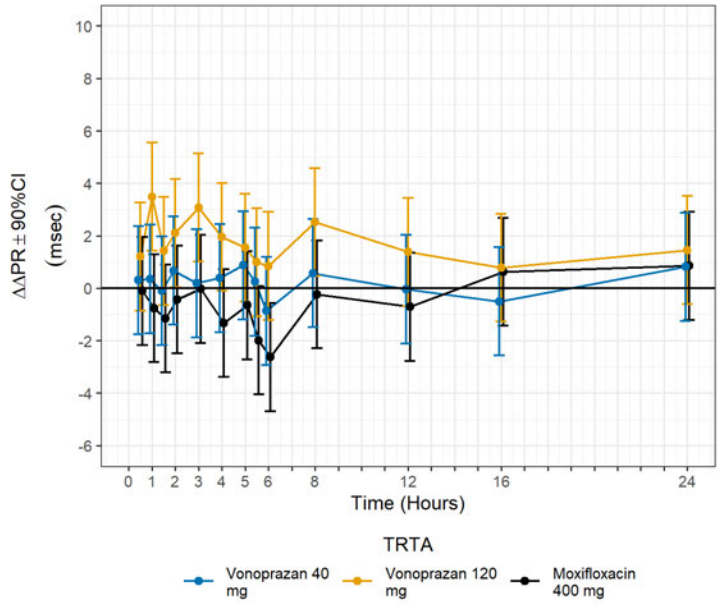
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of **ΔΔ**PR for different treatment groups.

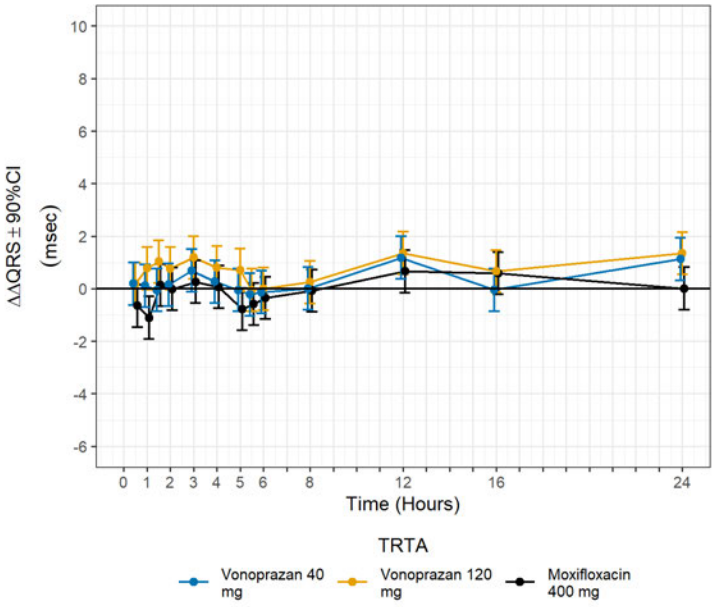
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of **ΔΔ**QRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of those subjects had observed QTcF above 450 msec. None of those subjects had observed ΔQTcF above 30 msec.

4.4.2 HR

None of those subjects had observed HR above 100 bpm.

4.4.3 PR

None of those subjects had observed PR above 220 msec with 25% increase over baseline.

4.4.4 QRS

None of those subjects had observed QRS above 120 msec.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK (n = 64). In each sequence, 16 subjects were recruited, and all received the 4 sequential treatments except for 1 subject in the DACB sequence who did not receive the placebo and vonoprazan treatments in periods 3 and 4 respectively. In total, the analysis dataset contained 3556 time matched PK/ECG

observations. Since vonoprazan metabolites are potentially ≥ 10% of total circulating moieties exploratory plots were used to assess potential relationships between dQTcF and concentration of vonoprazan and its metabolites. These plots indicated no potential relationships and therefore the metabolites were not considered in the subsequent linear mixed effect model.

4.5.1 QTc

Prior to evaluating the relationship between vonoprazan concentration and dQTcF using a linear mixed effects model, the three key assumptions of the model were evaluated using exploratory analysis. These assumptions include:

1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR);
2) absence of delay between plasma concentration and **ΔΔ**QTcF; and
3) absence of a nonlinear relationship.

Figure 2 shows the time-course of **ΔΔ**HR, with an absence of significant **ΔΔ**HR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and **ΔΔ**QTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model. Figure 5 shows that although Tmax is at 2 hours, mean of largest ddQTcF is observed 8 hours after dose and is < 5 msec.

Figure 5: ΔΔQTcFs versus time matched vonoprazan concentrations (hysteresis plot) for the 40 mg (red) and 120 mg (blue) doses respectively

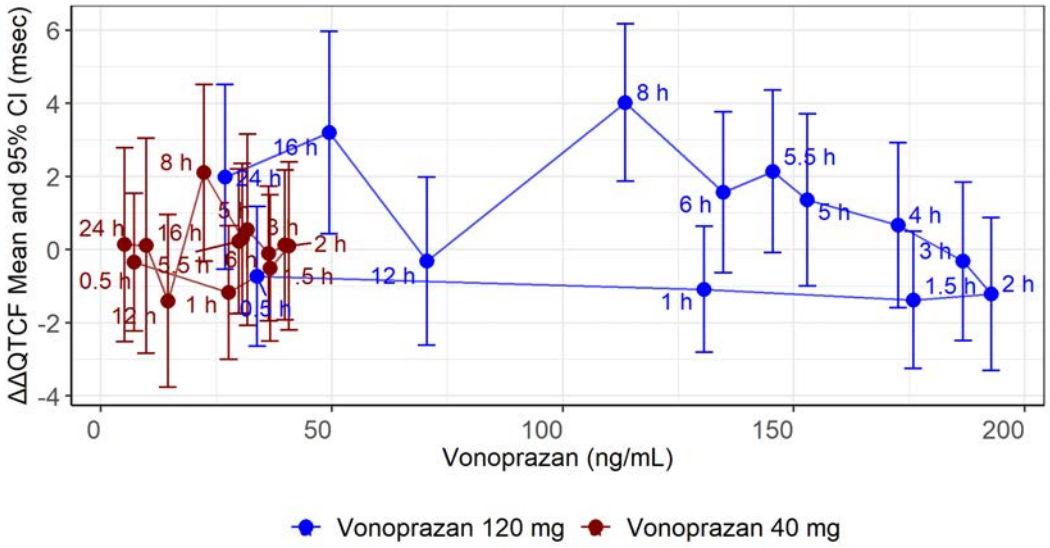
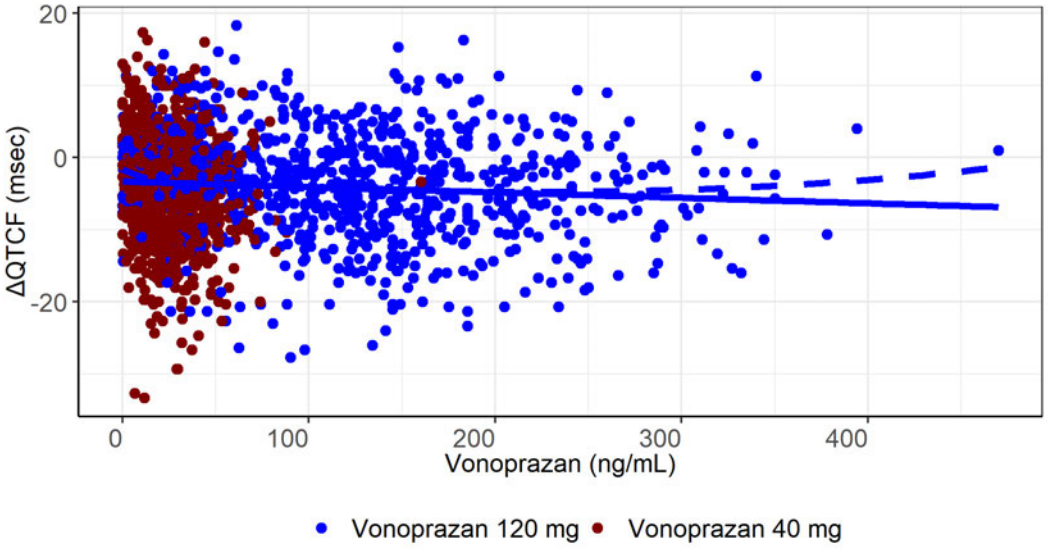


Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 4.

Figure 7: Goodness-of-fit Plot for QTcF

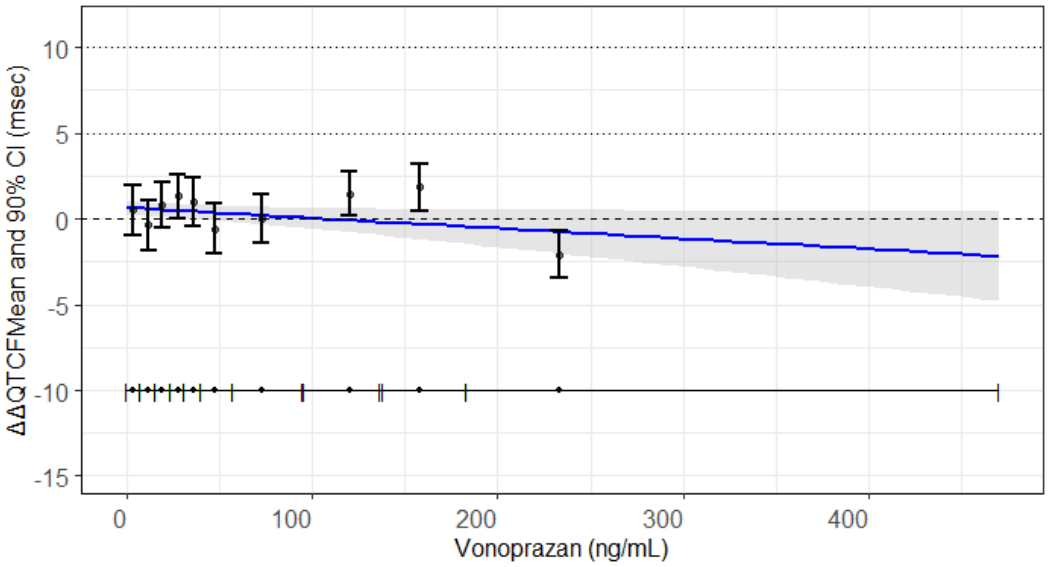


Table 4: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Vonoprazan (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Vonoprazan 40 mg	1	45.7	0.4	(-0.1 to 0.8)
Vonoprazan 120 mg	1	213.3	-0.6	(-1.8 to 0.5)

4.5.1.1 Assay Sensitivity

The time course of moxifloxacin concentration and ΔΔQTcF is shown in Figure 8. When the same linear mixed effect model is applied, the goodness-of-fit plot for moxifloxacin is

shown in Figure 9, and the predicted QTcF at the geometric mean Cmax is listed in Table 5. Assay sensitivity was also established using by-time analysis (Section 4.3.1.1).

Figure 8: ΔΔQTcFs versus time matched moxifloxacin concentrations (hysteresis plot) after 400 mg dose.

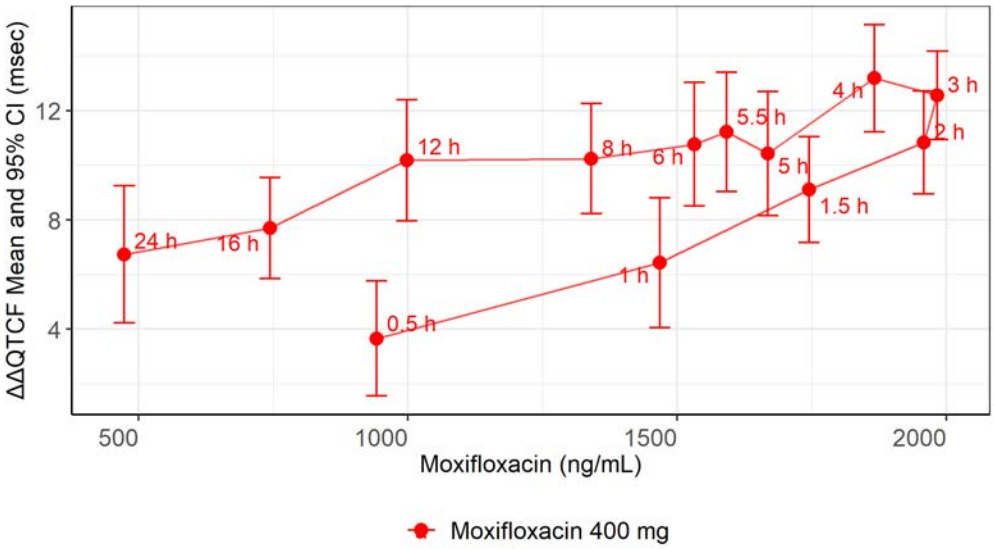


Figure 9: Goodness-of-fit plot of ΔΔQTcF for Moxifloxacin

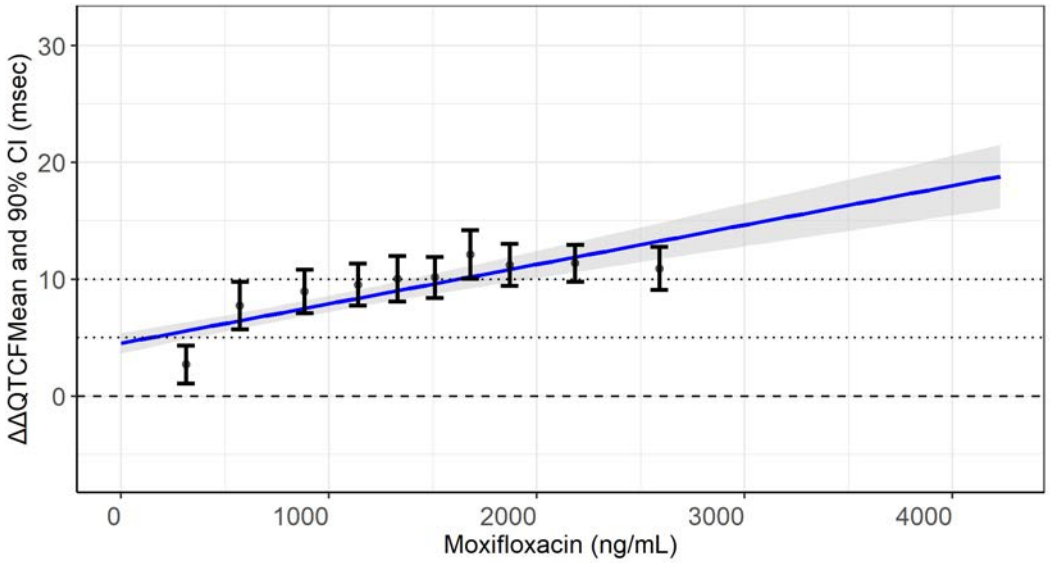


Table 5: Predictions from Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	2285.9	12.2	(10.9 to 13.6)

4.6 SAFETY ASSESSMENTS

See section 3.1.6. No additional safety analyses were conducted.

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/

YU YI HSU
02/10/2022 02:41:57 PM

DALONG HUANG
02/10/2022 02:47:53 PM

ELIFORD N KITABI
02/10/2022 02:51:19 PM

MICHAEL Y LI
02/10/2022 02:53:52 PM

LARS JOHANNESEN
02/11/2022 08:06:23 AM

CHRISTINE E GARNETT
02/11/2022 08:10:02 AM

MEMORANDUM

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

DATE: January 26, 2022

TO:
Leah Rosenfeld – Pharmacology Toxicology Reviewer
Terry Miller – Pharmacology Toxicology TL
Eva Zuffova, DAI - RPM

THROUGH:
Juli Tomaino, MD
Deputy Director, Division of Gastroenterology (DG)

FROM:
Laura Finkelstein, MD
Clinical Reviewer, DG

Joette Meyer, PharmD
Clinical Team Leader, DG

Dinesh Gautam, Ph.D.
Pharmacologist, PT-II

Jackye Peretz, Ph.D.
Lead Toxicologist, PT-II

Sushanta Chakder, Ph.D.
Supervisory Pharmacologist, PT-II

SUBJECT: Response to labeling consult request from Division of Anti-Infectives (DAI) regarding the Applicant's request for a new Established Pharmacologic Class (EPC) for vonoprazan.

APPLICATION/DRUG:

Application Type	**Number**	**Name of Drug**
NDA	215152	Co-package of vonoprazan tablets 20 mg/amoxicillin capsules, (b) (4) 500 mg/ clarithromycin tablets, (b) (4) 500 mg
NDA	215153	Co-package of vonoprazan tablets, (b) (4) 20 mg/ amoxicillin capsules, (b) (4) 500 mg
Sponsor	Phathom Pharmaceuticals	
Proposed indication	Treatment of *Helicobacter pylori*	

Background:

Vonoprazan is a new molecular entity currently under review by the Division of Anti-infectives (DAI) under NDAs 215152 and 215153 for treatment of *Helicobacter pylori* in combination with antibiotics (referencing INDs 143190 and 144399). (b) (4) [redacted] Vonoprazan has received regulatory approval in Japan and other countries in Asia and Latin America for indications of EE healing and maintenance, gastric ulcer/duodenal ulcer healing, and for the prevention of recurrence of a gastric or duodenal ulcer during nonsteroidal anti-inflammatory drugs or aspirin administration.

Vonoprazan acts to inhibit acid release into the gastric lumen through reversible potassium competitive binding at the luminal portion of the H+/K+-ATPase ("proton pump"). Currently approved drugs described as proton-pump inhibitors (PPIs) include the substituted benzimidazoles (e.g., dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) which act to suppress acid secretion through irreversible inactivation of the gastric H+/K+ ATPase.

Vonoprazan and other drugs in class, already approved outside the United States (e.g., revaprazan, tegoprazan), were developed to address perceived clinical limitations with PPIs, which have been observed to have a delayed onset of action, require an acidic environment for activation and display an inconsistent duration of acid suppression.[1] In addition, vonoprazan and related drugs have been described in the literature as not metabolized extensively by CYP2C19, which exhibits genetic polymorphism, in contrast to many of the PPIs, and therefore have less interindividual variability in their pharmacokinetics.[2]

Established Pharmacologic Class (EPC)
An FDA "Established Pharmacologic Class" (EPC) text phrase describes a pharmacologic class associated with an approved indication of an active moiety that the FDA has determined to be scientifically valid and clinically meaningful.

In January 2006, FDA published a final rule [commonly referred to the "Physician Labeling Rule" (PLR)] that amended the requirements for the content and format of the prescribing information for human prescription drug and biological products. The PLR regulations require the following statement to appear under the Indications and Usage heading in the Highlights of Prescribing Information if a drug is a member of an EPC [see 21 CFR 201.57(a)(6)]:

[1] Rawla, P, T Sunkara, A Ofosu and V Gaduputi (2018). "Potassium-Competitive Acid Blockers - Are They the Next Generation of Proton Pump Inhibitors?" World J Gastrointest Pharmacol Ther 9(7): 63-68.
[2] Mori, H and H Suzuki (2019). "Role of Acid Suppression in Acid-Related Diseases: Proton Pump Inhibitor and Potassium-Competitive Acid Blocker." J Neurogastroenterol Motil 25(1): 6-14.

(Drug) is a (FDA EPC text phrase) indicated for [indication(s)].

FDA's practice for establishing the EPC for a new drug is described in MAPP 7400.13[3] and the FDA Guidance on *Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information*.[4] EPC concepts and unique identifier codes are maintained in the Medication Reference Terminology Database (MED-RT).[5] A pharmacologic class is defined on the basis of any one of the following three attributes of the drug:

1. Mechanism of action (MOA) — Pharmacologic action at the receptor, membrane, or tissue level;
2. Physiologic effect (PE) — Pharmacologic effect at the organ, system, or whole body level;
3. Chemical structure (CS).

EPC is a pharmacologic class associated with an approved indication of an active moiety that the FDA has determined to be scientifically valid and clinically meaningful according to the following definitions:

- A *scientifically valid* pharmacologic class is one that is supported by submitted, documented, empiric evidence showing that the active moiety's pharmacologic class is known (not just assumed on a theoretical basis) and is relevant and specific to a drug product's indication.
- A *clinically meaningful* pharmacologic class is one where understanding of the pharmacologic effect enhances the ability of professionals to understand the physiologic basis of the drug product's indication or to anticipate undesirable effects that may be associated with the active moiety or pharmacologic class.

The EPC text phrase "proton pump inhibitor" was assigned to describe the class of substituted benzimidazole drugs which act at the gastric H+K+ ATP-ase, based on the mechanism of action at the gastric parietal cell membrane.

In the Highlights of Prescribing Information for NDAs 215152 and 215153, the Applicant has proposed an EPC text phrase of "potassium-competitive acid blocker" for vonoprazan.

[3] Retrievable from: http://sharepoint fda.gov/orgs/CDER-OND/PaT/PT%20Website%20WG/Shared%20Documents/files/mapps/7400.13.pdf
[4] Retrievable from: https://www fda.gov/regulatory-information/search-fda-guidance-documents/labeling-human-prescription-drug-and-biological-products-determining-established-pharmacologic-class
[5] Retrievable from: https://ncit nci nih.gov/ncitbrowser/pages/vocabulary.jsf?dictionary=MED-RT&version=2021_03_01

DAI Consult Request

On December 21, 2021, DAI sent a consult request to DG to obtain input on the following questions related to the Applicant's proposed EPC for vonoprazan:

1) Is vonoprazan most accurately described as a PPI?
2) If not, is "potassium-competitive acid blocker" an appropriate EPC for vonoprazan?
3) If not, please suggest one or more appropriate EPC(s) for vonoprazan.

Determining the Established Pharmacologic Class

Per the MaPP 7400.13, the pharmacologic class of a drug can be based on the MOA, physiologic effect, or chemical structure. These three attributes of vonoprazan, as compared to the PPIs, were considered in defining the most scientifically valid and clinically meaningful EPC for vonoprazan, as described below.

Mechanism of Action

By definition in the MaPP, the MOA is the pharmacologic action at the receptor, membrane, or tissue level. Vonoprazan acts to inhibit the gastric proton pump at the parietal cell membrane.

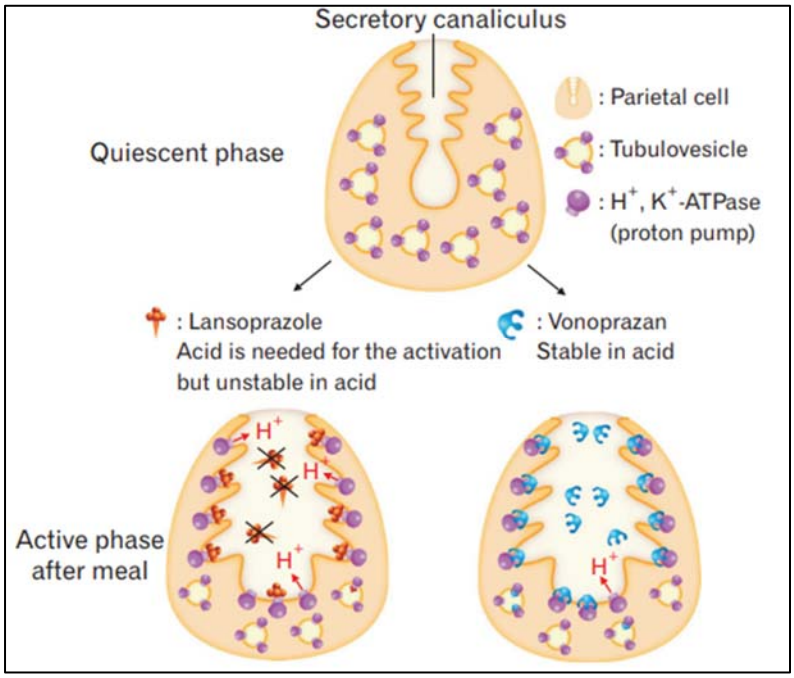
Although both vonoprazan and the currently approved PPIs inhibit the gastric proton pump to block acid release, the MOA by which vonoprazan inhibits the proton pump differs from the currently approved PPIs (see Figure 1). PPIs require activation by gastric acid and bind covalently to the gastric proton pump, with permanent deactivation of the proton pump. In contrast, vonoprazan reversibly and competitively binds the gastric proton pump without requiring gastric acid activation. (see the Appendix: Supportive Nonclinical Data)

The difference between how vonoprazan acts to inhibit the proton pump compared to the PPIs has potential clinical implications. Unlike vonoprazan, PPIs require activation, resulting in a delayed onset of action. Further, PPIs require an acidic environment and therefore, due to the therapeutic effect of increasing gastric pH, are self-inhibitory, whereas vonoprazan is active in both acidic and non-acidic environments.

Because they share a common site of pharmacologic effect, the selected EPC for vonoprazan should reflect the therapeutic similarities between the two drug classes without ignoring potentially clinically important differences. Assigning the same EPC to vonoprazan as the PPIs may not be appropriate, as inactivation of the proton pump incompletely describes its MOA (i.e., the reversible, ionically bound interaction with the luminal facing portion of the proton pump). The EPC for the approved PPIs is based on the MOA at the parietal cell membrane but does not describe clinical meaningful elements of the MOA including that the substituted benzimidazoles form irreversible, covalent disulfide bonds with the luminal facing portion of the proton pump. Therefore, we recommend "potassium-competitive proton pump inhibitor" as the EPC for vonoprazan.

The details of the specific mechanism of action for vonoprazan can be provided in Section 12.1 of the Prescribing Information to differentiate activity at the proton pump between vonoprazan and the substituted benzimidazoles for healthcare providers.

Figure 1: Gastric Acid Secretion



Source: (Oshima, 2018)[6]

Physiologic Effect

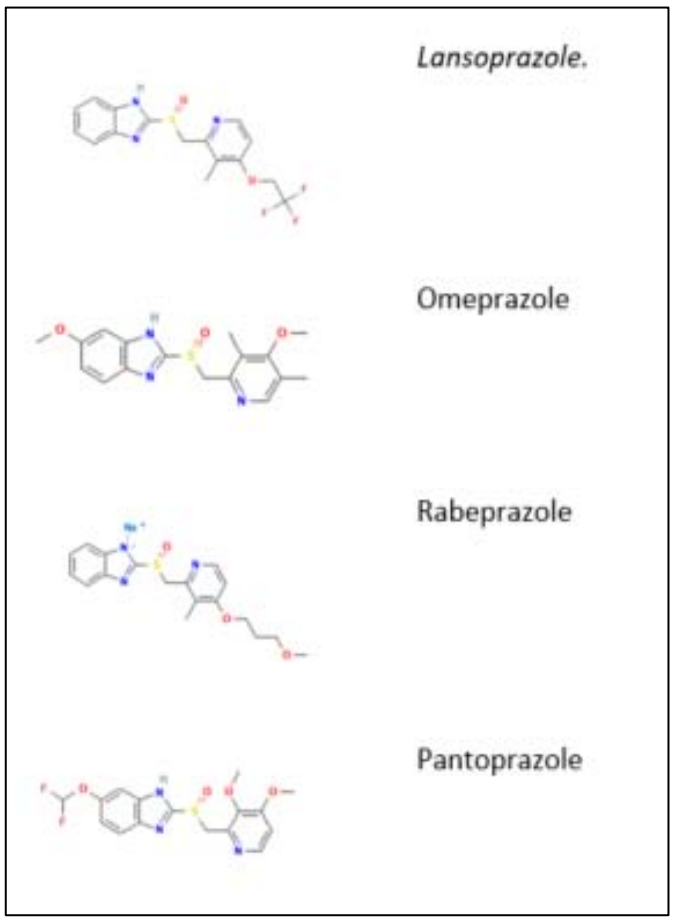
Both vonoprazan and the currently approved PPIs derive their physiologic effect through inhibition of the proton pump with resulting gastric acid suppression. As previously noted, this characterization provides insufficient information to aid healthcare providers in their clinical decision between use of vonoprazan or an approved PPI. Therefore, the EPC for vonoprazan should not be selected based solely on physiologic effect.

Chemical Structure

Vonoprazan and the PPIs are chemically distinct. All currently labeled PPIs are based around a benzimidazole structure (Figure 2) and are termed substituted benzimidazoles. Vonoprazan is a pyrrole derivative (Figure 3). However, the EPC for vonoprazan is most appropriately assigned based on MOA, rather than chemical structure, as the chemical structure is not of direct clinical importance.

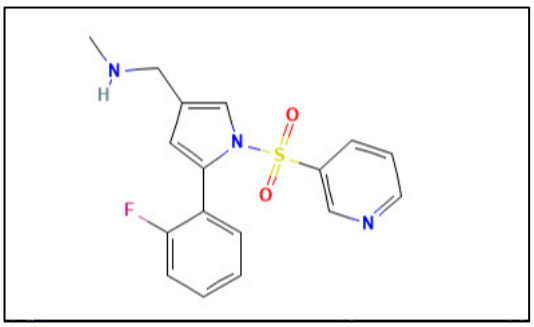
[6] Oshima, T and H Miwa (2018). "Potent Potassium-Competitive Acid Blockers: A New Era for the Treatment of Acid-Related Diseases." J Neurogastroenterol Motil **24**(3): 334-344.

Figure 2: Chemical Structures of Proton Pump Inhibitors (PPIs)



Source: Pub Chem[7]

Figure 3: Chemical Structure of Vonoprazan



Source: Pub Chem[8]

7 Retrievable at: https://pubchem.ncbi nlm nih.gov/#query=CID3883%20structure&tab=similarity
8 Retrievable at: https://pubchem.ncbi nlm nih.gov/compound/Vonoprazan#section=2D-Structure

Response to DAI Consult Questions

Question 1: Is vonoprazan most accurately described as a PPI?

Based upon our review, vonoprazan is not most accurately described as just a PPI. Section 12.1 of the prescribing information of the approved PPIs describe them as a class of antisecretory compounds that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell, and that this effect blocks the final step of acid production, leading to inhibition of both basal and stimulated gastric acid. This is true as well for vonoprazan, per the submitted pharmacological data (see Appendix: Supportive Nonclinical Data). Section 11 of the prescribing information of the approved PPIs also describes the PPI class as "substituted benzimidazole", which does not describe vonoprazan. The NCI Thesaurus (NCIt) further describes PPIs as "administered in the neutrally charged, *inactive form* and, upon entering the acidic environment of the parietal cell, *gets protonated and converted into its active form*. The active form will *covalently and irreversibly bind* to the proton pump".[9]

Given that vonoprazan inhibits the activity of the proton pump faster, more potently, and for a longer duration than the approved PPIs, vonoprazan should be distinguished from the approved PPIs. Further, given that vonoprazan is not a benzimidazole compound and does not require an acid medium for activation, it is not appropriately described solely as a PPI. However, because both vonoprazan and PPIs share a common site of pharmacologic activity and subsequent therapeutic effect, the commonalities should be included in the EPC designation, without implying that they are identical in clinical action. Therefore, we recommend "potassium-competitive proton pump inhibitor" as the EPC for vonoprazan.

DG acknowledges that the term "potassium-competitive acid blocker" and the acronym "PCAB" are accepted and understood by the scientific community and are used in the published scientific literature. Synonyms associated with the EPC "potassium competitive proton pump inhibitor" can exist in the Medical Reference Terminology database to provide a link between scientific terminology and regulatory nomenclature.

In addition, DG obtained input from Paul Brown, the OND Associate Director for Pharmacology and Toxicology, to better understand the implications of assigning an EPC to vonoprazan. Given the MOA of vonoprazan, the assigned EPC (either "potassium-competitive proton pump inhibitor" or "potassium-competitive acid blocker") would likely be categorized in the EPC hierarchy as a 'child' of the PPI EPC, which further establishes the relationship between the two drug classes and supports DG's proposed EPC.

Question 2: If not, is "potassium-competitive acid blocker" an appropriate EPC for vonoprazan?

[9] Emphasis added by reviewer. Retrievable from: https://ncit.nci nih.gov/ncitbrowser/pages/home.jsf.

We do not recommend "potassium-competitive acid-blocker" as the EPC for vonoprazan. Describing vonoprazan as a potassium-competitive acid blocker (PCAB) is a scientifically valid description of how vonoprazan inhibits the proton pump, with resulting reduction of acid secretion. However, the site of pharmacologic activity of vonoprazan that is shared with the approved PPIs, (i.e., at the proton pump) is not captured by the description of vonoprazan as a PCAB. As a result, the EPC of PCAB is not a complete, clinically meaningful description of vonoprazan (refer to MaPP 7400.13). On the other hand, describing vonoprazan as a "potassium-competitive proton pump inhibitor" provides healthcare providers with both a scientifically valid description of vonoprazan and clinically meaningful information about how vonoprazan relates to other therapeutic options.

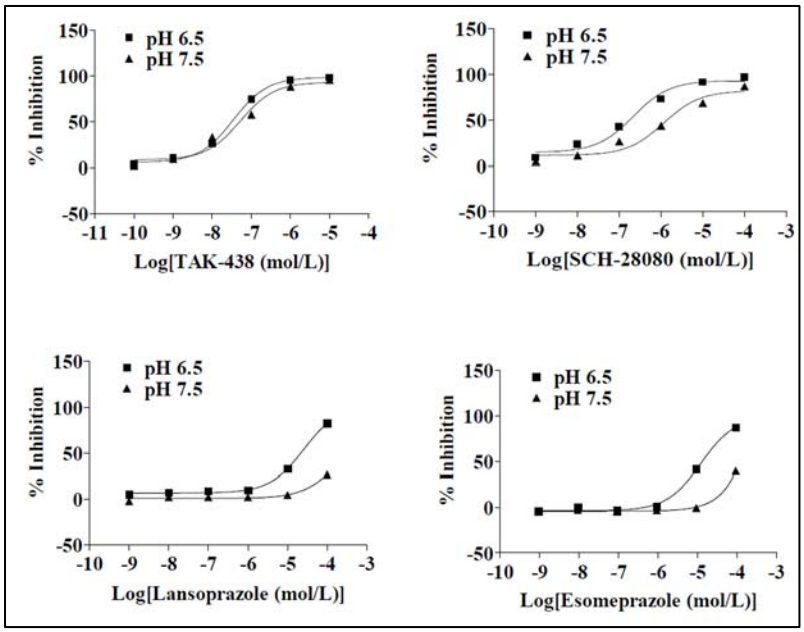
Question 3: If not, please suggest one or more appropriate EPC(s) for vonoprazan.

We recommend the EPC "potassium-competitive proton pump inhibitor" for vonoprazan. Please see the responses to Questions 1 and 2.

Appendix: Supportive Nonclinical Data

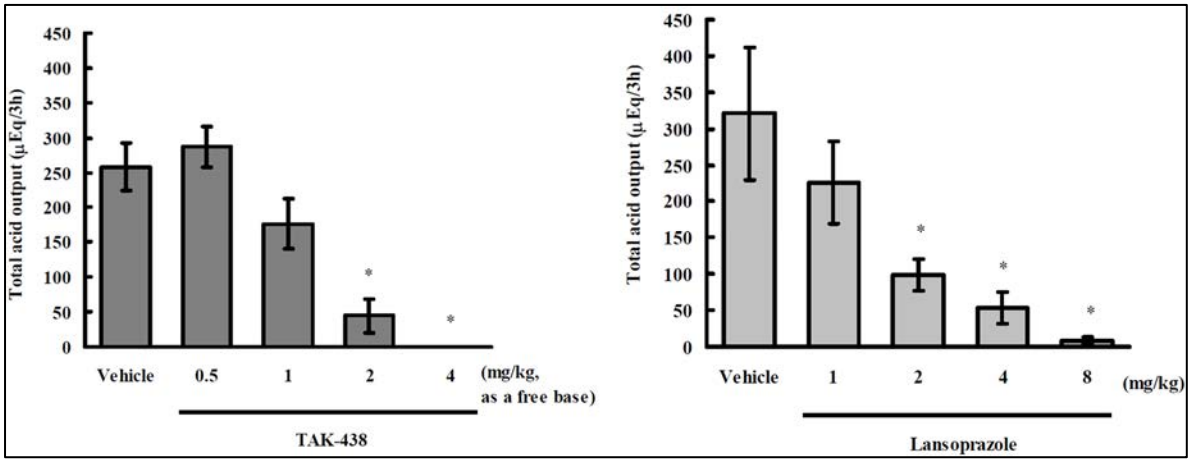
Vonoprazan (TAK-438) has been shown to inhibit the activity of the H^+,K^+-ATPase (proton pump) and subsequent basal and stimulated gastric acid production more potently than the approved PPIs (IC_{50} in nmol/L vs µmol/L; Figures 4-6), and improve gastric pH better (pH 6 vs PH 5.3) and with a sustained duration (>5 hours vs 2 hours) compared to the approved PPIs (Figure 7).

Figure 4: Inhibition of proton pump by TAK-438 and approved PPIs



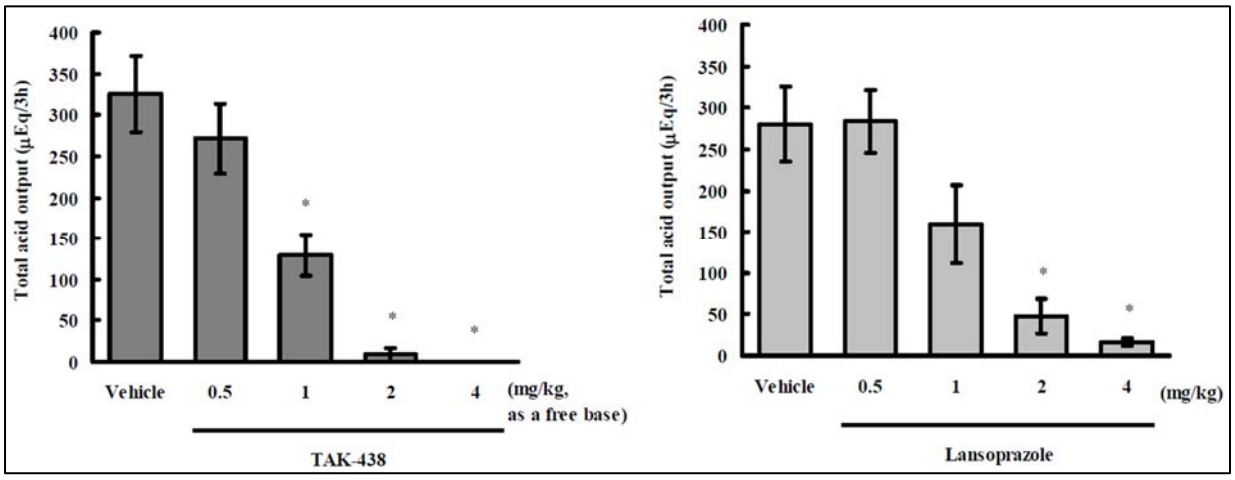
Source: Study TCAD2007-LA-01

Figure 5: Basal gastric acid production by TAK-438 and approved PPI



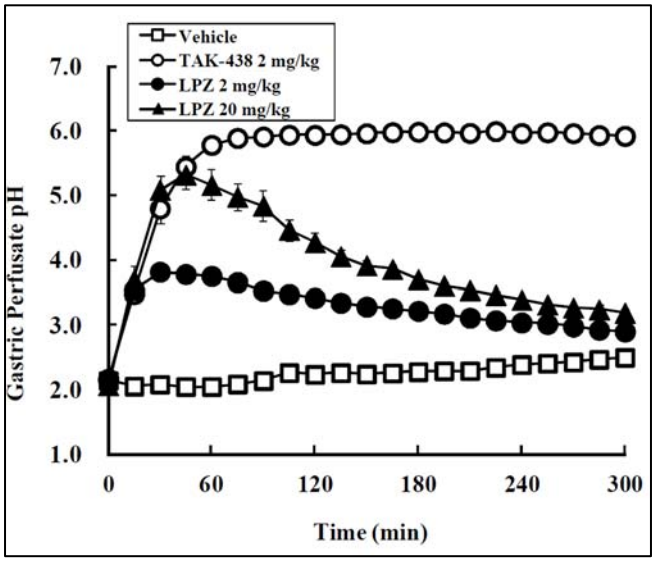
Source: Study SD1LA2006-NI-008, 009

Figure 6: Stimulated gastric acid production by TAK-438 and approved PPI



Source: SD1LA2006-NI-004, 005

Figure 7: Gastric pH over time with TAK-438 and approved PPI

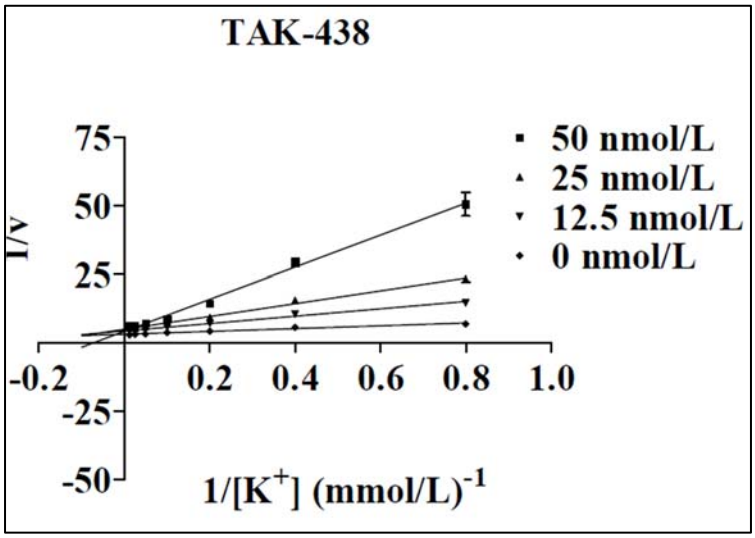


Source: Study SYLA2010-TY-001

Inhibition of the proton pump by TAK-438 occurs via a different mechanism of action than the approved PPIs. Unlike the approved PPIs which covalently bind to the luminal facing portion of the proton pump via disulfide bonds, TAK-438 ionically binds the proton pump competitively with potassium, evidenced by a decrease in in vitro proton pump inhibition with increasing concentrations of co-cultured potassium (Figure 8), and maintenance of proton pump inhibition in the presence of the thiol reagent, dithiothreitol (DTT; Figure 9). The binding of TAK-438 is potentially reversible as well, evidenced by the decrease in proton pump inhibition when a culture with TAK-438 was diluted 45-fold after initially inhibiting proton pump activity in rat

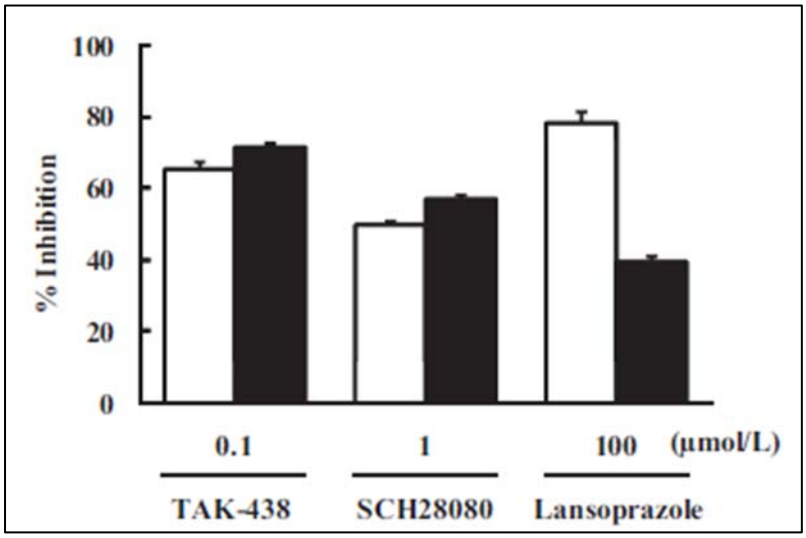
gastric parietal cells (Figure 10). Notably, the Applicant has not yet demonstrated that TAK-438 binds directly to the potassium channel adjacent to the gastric proton pump.

Figure 8: Lineweaver-Burk plot of competitive TAK-438 inhibition of proton pump with potassium



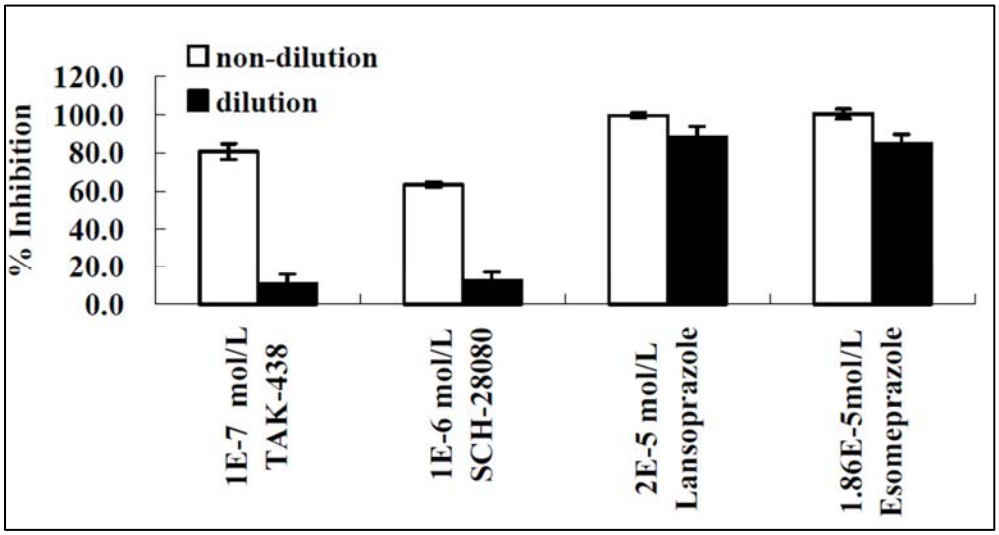
Source: Study TCAD2007-LA-03

Figure 9: Inhibition of proton pump by TAK-438 and approve PPI cultured with disulfide bond inhibiting compound, dithiothreitol (black bars)



Source: Hori Y, et al., 2010;335(1):231–8

Figure 10: Reversibility of proton pump inhibition by TAK-438 and approved PPIs



Source: Study TCAD2007-LA-02

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/

LAURA H FINKELSTEIN
01/26/2022 01:47:37 PM

JACKYE R PERETZ
01/26/2022 01:55:38 PM

SUSHANTA K CHAKDER
01/26/2022 03:22:04 PM

JOETTE M MEYER
01/26/2022 04:31:14 PM

JULI A TOMAINO
01/26/2022 05:11:36 PM

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:	December 9, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215152 and NDA 215153
Product Name and Strength:	(b) (4) Triple Pak (vonoprazan, amoxicillin, and clarithromycin) vonoprazan tablets, 20 mg; amoxicillin capsules, 500 mg; and clarithromycin tablets, 500 mg (b) (4) Dual Pak (vonoprazan and amoxicillin) vonoprazan tablets, 20 mg and amoxicillin capsules, 500 mg
Product Type:	Multi-Ingredient Products
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Phathom Pharmaceuticals, Inc.
FDA Received Date:	September 3, 2021
OSE RCM #:	2021-1750 and 2021-1752
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

Phathom Pharmaceuticals, Inc. is developing [(b) (4)] Triple Pak (vonoprazan, amoxicillin, and clarithromycin) and [(b) (4)] Dual Pak (vonoprazan and amoxicillin) for the treatment of H. pylori infection under NDA 215152 and NDA 215153, respectively. Thus, the Division of Anti-Infectives (DAI) requested that we review the proposed [(b) (4)] Triple Pak and [(b) (4)] Dual Pak prescribing information (PI), container labels, carton labeling, professional sample container labels, and professional sample carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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

We note that the Applicant intends to market [(b) (4)] Triple Pak and [(b) (4)] Dual Pak under a single Prescribing Information (PI). The proposed PI, container labels, carton labeling, professional sample container labels, and professional sample 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 Sections 5 and 6 for Phathom Pharmaceuticals, Inc. for [(b) (4)] Triple Pak and [(b) (4)] Dual Pak, respectively.

4 RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Highlights of Prescribing Information			
1.	In Section 2, Dosage and Administration, the dosage of amoxicillin for both (b) (4) Triple Pak and (b) (4) Dual Pak is listed as "1000 mg".	The use of a comma in large numbers can help prevent a 10-fold dosing error. For example, the use of a comma in the number "1,000" can help prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000".	Revise the dose of amoxicillin to read "1,000 mg".
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, the dosage of amoxicillin for both (b) (4) Triple Pak and (b) (4) Dual Pak is listed as "1000 mg".	The use of a comma in large numbers can help prevent a 10-fold dosing error. For example, the use of a comma in the number "1,000" can help prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000".	Revise the dose of amoxicillin to read "1,000 mg".

5 RECOMMENDATIONS FOR PHATHOM PHARMACEUTICALS, INC. REGARDING (b) (4) TRIPLE PAK

Table 3. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. Regarding (b) (4) Triple Pak (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label and Professional Sample Blister Label			
1.	The lot number and expiration date are missing.	The lot number and expiration date are required on the immediate container per 21 CFR	Note the placement of the lot number statement and the placement and format of the expiration date.

Table 3. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. Regarding (b) (4) Triple Pak (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		201.10(i) and 21 CFR 201.17, respectively.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and 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.
2.	The linear barcode is absent.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product's linear barcode to each individual container as required per 21 CFR 201.25(c)(2). Ensure the barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25.(c)(i).
3.	As currently presented on the container label, the statements (b) (4) (b) (4) (b) (4)" " (b) (4)	Lack of clarity may cause misinterpretation of the statements to mean that the collective quantity of respective dosage units	Update the label to indicate the strength per dosage unit. For example, revise to read: "2 vonoprazan tablets, 20 mg per tablet*"

Table 3. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. Regarding [(b) (4)] Triple Pak (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	[(b) (4)] and "[(b) (4)]" could lead to confusion because it is unclear whether each individual dosage unit contains the specified amount of active ingredient.	equals the total strength indicated (e.g., misinterpretation that two vonoprazan tablets equate to 20 mg, etc.). Indicating the strength per dosage unit would increase clarity and help mitigate dosing and administration errors.	"4 amoxicillin capsules, [(b) (4)] 500 mg per capsule**" "2 clarithromycin tablets, [(b) (4)] 500 mg per tablet"
Carton Labeling and Professional Sample Carton Labeling			
1.	As currently presented, the carton labeling does not contain a product identifier.	In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data	We recommend that you review the guidance, *Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers (July 2021)*, to determine if the product identifier requirements apply to your product's labeling.[a]

[a] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers, July 2021. Available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 3. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. Regarding [(b) (4)] Triple Pak (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		matrix barcode) format. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode. NDC: [insert product's NDC] SERIAL: [insert product's serial number] LOT: [insert product's lot number] EXP: [insert product's expiration date]	
2.	As currently presented on the side panel of the carton, the statements [(b) (4)] could lead to confusion because it is unclear whether each individual dosage unit contains the specified amount of active ingredient.	Lack of clarity may cause misinterpretation of the statements to mean that the collective quantity of respective dosage units equals the total strength indicated (e.g., misinterpretation that two vonoprazan tablets equate to 20 mg, etc.). Indicating the strength per dosage unit would increase clarity and help mitigate dosing and administration errors.	Update the labeling to indicate the strength per dosage unit. For example, revise to read: "2 vonoprazan tablets, 20 mg per tablet*" "4 amoxicillin capsules, [(b) (4)] 500 mg per capsule**" "2 clarithromycin tablets, [(b) (4)] 500 mg per tablet"

6 RECOMMENDATIONS FOR PHATHOM PHARMACEUTICALS, INC. REGARDING (b) (4) DUAL PAK

Table 4. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. Regarding (b) (4) Dual Pak (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label and Professional Sample Blister Label			
1.	The lot number and expiration date are missing.	The lot number and expiration date are required on the immediate container per 21 CFR 201.10(i) and 21 CFR 201.17, respectively.	Note the placement of the lot number statement and the placement and format of the expiration date. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and 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.
2.	As currently presented, the directions on the back of the container label currently instruct patients to (b) (4)	Instructions that are incongruent with what patients visualize on the blister pack may lead to confusion and dosing errors.	Improve the graphics of the blister pack by adding an indicator for where the patient is supposed to cut. This can be done by adding a scissors sign,

Table 4. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. Regarding (b) (4) Dual Pak (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	(b) (4) However, there are no "scissor markings" on the blister pack indicating where patients should cut.		such as what is currently on the backside of (b) (4) Triple Pak.
3.	As currently presented, by following the directions to " (b) (4) a patient may cut the blister pack with scissors directly beneath the directions but above the "AM" dose, severing the blister pack into two pieces.	The directions located at the top of the blister pack may become separated from the "MID-DAY" and "PM" doses, leading to confusion and dosing errors.	Reorient the dosing schedule presentation on the blister pack. "AM", "MID-DAY", and "PM" to appear in an orientation from left to right, similar to how the dosing schedule is oriented on the (b) (4) Triple Pak. Alternatively, consider flipping the positions of the "AM" and "PM" wording, so that "PM" is listed immediately below the directions and that "AM" is listed at the bottom of the blister pack. Thus, if a patient were to sever the blister completely when taking their AM dose, the "MID-DAY" and "PM" doses would still be attached to the directions portion of the blister pack. Similarly, if the patient were to sever the blister completely when taking their MID-DAY dose, the "PM" dose would still be attached to the directions.
4.	The linear barcode is absent.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore,	Add the product's linear barcode to each individual container as required per 21 CFR 201.25(c)(2). Ensure the barcode is surrounded by

Table 4. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. Regarding (b) (4) Dual Pak (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		it is an important safety feature that should be part of the label whenever possible.	sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25.(c)(i).
5.	As currently presented on the container label, the statements "(b) (4) (b) (4) could lead to confusion because it is unclear whether each individual dosage unit contains the specified amount of active ingredient.	Lack of clarity may cause misinterpretation of the statements to mean that the collective quantity of respective dosage units equals the total strength indicated (e.g., misinterpretation that two vonoprazan tablets equate to 20 mg, etc.). Indicating the strength per dosage unit would increase clarity and help mitigate dosing and administration errors.	Update the labeling to indicate the strength per dosage unit. For example, revise to read: "2 vonoprazan tablets, 20 mg per tablet*" "6 amoxicillin capsules, (b) (4) 500 mg per capsule**"
Carton Labeling and Professional Sample Carton Labeling			
1.	As currently presented, the carton labeling does not contain a product identifier.	In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning	We recommend that you review the guidance, *Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers (July 2021)*, to determine if the product identifier requirements apply to your product's labeling.[b]

[b] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers, July 2021. Available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 4. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. Regarding [redacted] Dual Pak (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		November 27, 2017, and November 27, 2018, respectively. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode. NDC: [insert product's NDC] SERIAL: [insert product's serial number] LOT: [insert product's lot number] EXP: [insert product's expiration date]	
2.	As currently presented, the carton labeling displays an incorrect amount of amoxicillin capsules present in one daily blister pack (i.e., [redacted] capsules).	An incorrect value of amoxicillin capsules printed on the carton labeling could cause confusion and lead to medication errors.	Correct the carton labeling to state: "Each Daily Treatment Pack Contains: 2 vonoprazan tablets, 20 mg* 6 amoxicillin capsules, [redacted] 500 mg***"
3.	As currently presented on the side panel of the carton, the statements [redacted] could lead to confusion because it is	Lack of clarity may cause misinterpretation of the statements to mean that the collective quantity of respective dosage units equals the total strength indicated (e.g., misinterpretation that two	Update the labeling to indicate the strength per dosage unit. For example, revise to read: "2 vonoprazan tablets, 20 mg per tablet*" "6 amoxicillin capsules, [redacted] 500 mg per capsule**"

Table 4. Identified Issues and Recommendations for Phathom Pharmaceuticals, Inc. Regarding (b) (4) Dual Pak (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	unclear whether each individual dosage unit contains the specified amount of active ingredient.	vonoprazan tablets equate to 20 mg, etc.). Indicating the strength per dosage unit would increase clarity and help mitigate dosing and administration errors.	

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for (b) (4) Triple Pak that Phathom Pharmaceuticals, Inc. submitted on September 3, 2021, and the listed drugs (LD).

Table 5. Relevant Product Information for Listed Drugs and (b) (4) Triple Pak

Product Name	**Amoxil**	**Biaxin**	(b) (4) Triple Pak
Initial Approval Date	January 18, 1974	October 21, 1991	N/A
Active Ingredient	Amoxicillin	Clarithromycin	Vonoprazan, amoxicillin, and clarithromycin
Indication	Treatment of infections due to susceptible (ONLY B-lactamase negative) strains of the designated microorganisms in the conditions listed below: • Infections of the ear, nose, and throat – due to Streptococcus spp., S. pneumoniae, Staphylococcus spp,. Or H. influenzae • Infections of the genitourinary tract – due to E. coli, P. mirabilis, or E. faecalis • Infections of the skin and skin structure – due to Streptococcus spp., Staphylococcus spp., or E. coli • Infections of the lower respiratory tract – due to Streptococcus spp., S. pneumoniae, Staphylococcus spp., Or H. influenzae	Acute Bacterial Exacerbation of Chronic Bronchitis caused by susceptible isolated due to H. influenzae, H. parainfluenzae, M. catarrhalis, or S. pneumoniae Acute Maxillary Sinusitis caused by susceptible isolates due to H. influenzae, M. catarrhalis, or S. pneumoniae Community-Acquired Pneumonia caused by susceptible isolated due to H. influenzae, H. parainfluenzae, M. catarrhalis, M. pneumoniae, S. pneumoniae, C. pneumoniae Pharyngitis/Tonsillitis caused by susceptible isolates due to S. pyogenes	Treatment of H. pylori infection in adults

<table>
<tr>
<td></td>
<td>

Gonorrhea, acute uncomplicated (ano-genital and urethral infections) – due to N. gonorrhoeae
H. pylori eradication to reduce the risk of duodenal ulcer recurrence

</td>
<td><u>Uncomplicated Skin and Skin Structure Infections</u> caused by susceptible isolates due to S. aureus or S. pyogenes

<u>Acute Otitis Media</u> caused by susceptible isolates due to H. influenzae, M. catarrhalis, or S. pneumoniae

<u>Treatment and prophylaxis of disseminated Mycobacterial Infections</u> caused by susceptible isolates due to M. avium or M. intracellulare in patients with advanced HIV infection

<u>Helicobacter pylori Infection and Duodenal Ulcer Disease</u></td>
<td></td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Capsule, chewable tablets, and oral suspension</td>
<td>Filmtab, granules for oral suspension</td>
<td>Tablet (vonoprazan), tablet (clarithromycin), and capsule (amoxicillin)</td>
</tr>
<tr>
<td>Strength</td>
<td>Capsule: 500 mg
Oral suspension: 250 mg/5 mL, 400 mg/5mL
Pediatric drops for oral suspension: 50 mg/mL</td>
<td>Filmtab: 250 mg, 500 mg
XL Filmtab: 500
Granules for oral suspension: 125 mg/5 mL, 250 mg/5mL</td>
<td>Vonoprazan 20 mg
Amoxicillin 500 mg
Clarithromycin 500 mg</td>
</tr>
<tr>
<td>Dose and Frequency</td>
<td><u>Neonates and Infants Ages ≤ 12 weeks (≤ 3 months)</u>: recommended upper dose is 30 mg/kg/day divided q12h</td>
<td><u>Adult Dosage</u>:
<table>
<tr><td></td><td colspan="2">Biaxin Filmtab</td><td colspan="2">Biaxin XL Filmtab</td></tr>
<tr><td>Infection</td><td>Dosage (every</td><td>Duration (days)</td><td>Dosage (every</td><td>Duration (days)</td></tr>
</table>
</td>
<td>Vonoprazan 20 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg, each given twice daily, for</td>
</tr>
</table>

Adults and Pediatric Patients > 3 months:

Infection	Severity	Usual Adult Dose	Usual Dose for Children > 3 months
Ear/nose/ throat	Mild/ moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours OR 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours OR 40 mg/kg/day in divided doses every 8 hours
Lower respiratory tract	Mild/ moderate or severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours OR 40 mg/kg/day in divided doses every 8 hours
Skin/skin structure	Mild/ moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours OR 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12	45 mg/kg/day in divided

	12 hours)		24 hours)	
Acute bacterial exacerbation of chronic bronchitis	250 to 500 mg	7-14	1 g	7
Acute maxillary sinusitis	500 mg	14	1 g	14
Community acquired pneumonia	250 mg	7-14	1 g	7
Pharyngitis/ Tonsillitis	250 mg	10	-	-
Uncomplicated skin and skin structure infections	250 mg	7-14	-	-
Treatment and prophylaxis of disseminated M. avium disease	500 mg	-	-	-
H. pylori eradication to reduce risk of duodenal ulcer recurrence with amoxicillin and omeprazole	500 mg	10-14	-	-

14 days to be taken in the morning and evening with or without food

		hours or 500 mg every 8 hours	doses every 12 hours OR 40 mg/kg/day in divided doses every 8 hours
Genitourinary tract	Mild/ moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours OR 20 mg/kg/day in divided doses every 8 hours
Gonorrhea Acute, uncomplicated ano-genital and urethral infections in males and females		3 grams as a single oral dose	Prepubertal children: 50 mg/kg, combined with 25 mg/kg probenecid as a single dose. Probenecid is contraindicated in children under 2 years.

<u>H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence:</u>
Triple Therapy: Amoxil 1 mg/clarithromycin 500 mg/lansoprazole 30 mg every 12 hours for 14 days

Dual Therapy: Amoxil 1 gram/lansoprazole 30 mg, each given every 8 hours for 14 days

or lansoprazole				
H. pylori eradication to reduce the risk of duodenal ulver recurrence with omeprazole	500 mg every 8 hours	14	-	-

How Supplied	Capsules: 500 mg bottles of 500 Oral suspension: 250 mg/5 mL 100 mL bottle 250 mg/5 mL 150 mL bottle 400 mg/5 mL 100 mL bottle Pediatric drops for oral suspension: 50 mg/mL 30 mL bottle	Filmtab: 250 mg and 500 mg: bottles of 60 and unit dose strip packages of 100 XL Filmtab: 500 mg tablets: bottles of 60 and unit dose strip packages of 10, and Biaxin XL Pac carton of 4 blister packages 14 tablets each Granules for oral suspension: 125 mg/5 mL and 250 mg/5 ml: 50 mL bottle and 100 mL bottle	Carton containing 14 individual daily administration packs. Each administration pack contains: • Two vonoprazan 20 mg tablets • Four amoxicillin 500 mg capsules • Two clarithromycin 500 mg tablets
Storage	Store 500 mg capsules and 250 mg unreconstituted powder at or below 20 °C (68 °F) Store 400 mg unreconstituted powder at or below 25 °C (77 °F)	Store Filmtab at 20 °C to 25 °C (68 ° F to 77 °F). Excursions permitted to 15 ° C to 30 °C (59 °F to 86 °F) Store granules for oral suspension below 25 °C (77 °F) in a well-closed container. Do not refrigerate the reconstituted granules.	Between 20 °C to 25 °C (68 °F to 77°F)

Table 6 presents relevant product information for (b) (4) Dual Pak that Phathom Pharmaceuticals, Inc. submitted on September 3, 2021, and the listed drug.

Table 6. Relevant Product Information for Listed Drug and (b) (4) Dual Pak

Product Name	**Amoxil**	(b) (4) Dual Pak
Initial Approval Date	January 18, 1974	N/A
Active Ingredient	Amoxicillin	Vonoprazan and amoxicillin
Indication	Treatment of infections due to susceptible (ONLY B-lactamase negative) strains of the designated microorganisms in the conditions listed below: • Infections of the ear, nose, and throat – due to Streptococcus spp., S. pneumoniae, Staphylococcus spp,. Or H. influenzae	Treatment of H. pylori infection in adults

<table>
<tr><td></td><td>

Infections of the genitourinary tract – due to E. coli, P. mirabilis, or E. faecalis
Infections of the skin and skin structure – due to Streptococcus spp., Staphylococcus spp., or E. coli
Infections of the lower respiratory tract – due to Streptococcus spp., S. pneumoniae, Staphylococcus spp., Or H. influenzae
Gonorrhea, acute uncomplicated (ano-genital and urethral infections) – due to N. gonorrhoeae

H. pylori eradication to reduce the risk of duodenal ulcer recurrence
</td><td></td></tr>
<tr><td>Route of Administration</td><td>Oral</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>Capsule, chewable tablets, and oral suspension</td><td>Tablet (vonoprazan) and capsule (amoxicillin)</td></tr>
<tr><td>Strength</td><td>Capsule: 500 mg
Oral suspension: 250 mg/5 mL, 400 mg/5mL
Pediatric drops for oral suspension: 50 mg/mL</td><td>Vonoprazan 20 mg
Amoxicillin 500 mg</td></tr>
<tr><td>Dose and Frequency</td><td><u>Neonates and Infants Ages ≤ 12 weeks (≤ 3 months)</u>: recommended upper dose is 30 mg/kg/day divided q12h

<u>Adults and Pediatric Patients > 3 months</u>:
<table>
<tr><th>Infection</th><th>Severity</th><th>Usual Adult Dose</th><th>Usual Dose for Children > 3 months</th></tr>
<tr><td rowspan="2">Ear/nose/ throat</td><td>Mild/ moderate</td><td>500 mg every 12 hours or 250 mg every 8 hours</td><td>25 mg/kg/day in divided doses every 12 hours OR 20 mg/kg/day in divided doses every 8 hours</td></tr>
<tr><td>Severe</td><td>875 mg every 12 hours or 500 mg every 8 hours</td><td>45 mg/kg/day in divided doses every 12 hours OR 40 mg/kg/day in divided doses every 8 hours</td></tr>
<tr><td>Lower respiratory tract</td><td>Mild/ moderate or severe</td><td>875 mg every 12 hours or 500 mg every 8 hours</td><td>45 mg/kg/day in divided doses every 12 hours OR 40 mg/kg/day in divided doses every 8 hours</td></tr>
</table>
</td><td>Vonoprazan 20 mg given twice daily (morning and evening) and amoxicillin 1,000 mg given three times daily (morning, mid-day, and evening), for 14 days to be taken in the with or without food</td></tr>
</table>

<table>
<tr>
<td></td>
<td>
<table>
<tr><td>Skin/skin structure</td><td>Mild/ moderate</td><td>500 mg every 12 hours or 250 mg every 8 hours</td><td>25 mg/kg/day in divided doses every 12 hours OR 20 mg/kg/day in divided doses every 8 hours</td></tr>
<tr><td></td><td>Severe</td><td>875 mg every 12 hours or 500 mg every 8 hours</td><td>45 mg/kg/day in divided doses every 12 hours OR 40 mg/kg/day in divided doses every 8 hours</td></tr>
<tr><td>Genitourinary tract</td><td>Mild/ moderate</td><td>500 mg every 12 hours or 250 mg every 8 hours</td><td>25 mg/kg/day in divided doses every 12 hours OR 20 mg/kg/day in divided doses every 8 hours</td></tr>
<tr><td>Gonorrhea

Acute, uncomplicated ano-genital and urethral infections in males and females</td><td></td><td>3 grams as a single oral dose</td><td>Prepubertal children: 50 mg/kg, combined with 25 mg/kg probenecid as a single dose. Probenecid is contraindicated in children under 2 years.</td></tr>
</table>
<u>H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence:</u>
Triple Therapy: Amoxil 1 mg/clarithromycin
500 mg/lansoprazole 30 mg every 12 hours for 14 days

Dual Therapy: Amoxil 1 gram/lansoprazole 30 mg, each given every 8 hours for 14 days
</td>
<td></td>
</tr>
<tr>
<td>How Supplied</td>
<td>Capsules: 500 mg bottles of 500

Oral suspension: 250 mg/5 mL 100 mL bottle
250 mg/5 mL 150 mL bottle
400 mg/5 mL 100 mL bottle

Pediatric drops for oral suspension: 50 mg/mL 30 mL bottle</td>
<td>Carton containing 14 individual daily administration packs. Each administration pack contains:
• Two vonoprazan 20 mg tablets
• Six amoxicillin 500 mg capsules</td>
</tr>
<tr>
<td>Storage</td>
<td>Store 500 mg capsules and 250 mg unreconstituted powder at or below 20 °C (68 °F)
Store 400 mg unreconstituted powder at or below 25 °C (77 °F)</td>
<td>Between 20 °C to 25 °C (68 °F to 77°F)</td>
</tr>
</table>

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,[c] along with postmarket medication error data, we reviewed the following (b) (4) Triple Pak and (b) (4) Dual Pak labels and labeling submitted by Phathom Pharmaceuticals, Inc.

- Container labels received on September 3, 2021
- Carton labeling received on September 3, 2021
- Professional Sample Blistercards received on September 3, 2021
- Professional Sample Carton Labeling received on September 3, 2021
- Prescribing Information (Image not shown) received on September 3, 2021, available from \\CDSESUB1\evsprod\nda215152\0002\m1\us\annotated-draft-labeling-text-apc221-v1.pdf

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

8 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

DAMON A BIRKEMEIER
12/09/2021 10:52:59 AM

MISHALE P MISTRY on behalf of VALERIE S VAUGHAN
12/09/2021 10:58:38 AM