

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215152Orig1s000

215153Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215152

Assessment # 1 - Addendum

Drug Product Name	VOQUEZNA TRIPLE PAK* (vonoprazan tablets; amoxicillin capsules; clarithromycin tablets)
Dosage Form	Tablets and capsules
Strength	20 mg; 500 mg; 500 mg (<i>respectively</i>)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Phathom Pharmaceuticals, Inc.
US agent, if applicable	N/A

*Proposed trade name

Submission(s) Assessed	Document Date	Discipline(s) Affected
0002	September 3, 2021	All
0012	December 17, 2021	Drug Substance, Drug Product, Process, Biopharmaceutics
0018	January 18, 2022	Drug Substance, Drug Product, Process
0020	January 24, 2022	Process
0021	January 25, 2022	Biopharmaceutics
0024	January 31, 2022	Environmental Assessment
0030	February 17, 2022	Drug Product
0039	April 8, 2022	Drug Product
0041	April 21, 2022	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Karina Zuck	Katherine Windsor
Drug Product	Molly Lee	Dorota Matecka
Manufacturing	Jiao Yang	Steve Rhieu
Microbiology	Jiao Yang	Steve Rhieu
Biopharmaceutics	Min Kang	Elsbeth Chikhale
Environmental Analysis	James Laurenson (<i>refer to Drug Product Review</i>)	
Laboratory (OTR)	N/A	
RBPM	Anh-Thy Ly	
ATL	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs*:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	September 2, 2021	Review by Dr. Udofot
	II			Adequate	October 19, 2021	Review by Dr. David Amspacher
	III				N/A*	
	III				N/A*	

*Sufficient information provided in the NDA – refer to the Drug Product Chapter

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
IND	143190	Development of triple therapy pack
ANDA	64076	Amoxicillin capsules used in the co-package (LoA provided in the NDA)
ANDA	65136	Clarithromycin tablets used in the co-package (LoA provided in the NDA)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	Adequate (acceptance criteria for impurities)	Refer to Drug Substance and Drug Product reviews	Dr. Leah Rosenfeld
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product (co-packaged vonoprazan tablets, amoxicillin capsules and clarithromycin tablets). In addition, all manufacturing and testing facilities have been found acceptable by the Office of Pharmaceutical Manufacturing Assessment (OPMA). Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

VOQUEZNA TRIPLE PAK is a co-packaged product containing vonoprazan, a potassium-competitive acid blocker (PCAB), amoxicillin, a penicillin class antibacterial, and clarithromycin, a macrolide antimicrobial, indicated for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults. Specifically, the proposed commercial drug product (triple therapy pack) contains: vonoprazan tablets, 20 mg, and previously approved, amoxicillin capsules, 500 mg, and clarithromycin tablets, 500 mg, all co-packaged in one blister card, on which each tablet or capsule is contained within its own blister cavity.

The proposed drug product combination received Fast Track (FT) and Qualified Infectious Disease Product (QIDP) designations on January 22, 2021 and May 16, 2021, respectively (for the treatment of *Helicobacter pylori* infection).

Proposed Indication(s) including Intended Patient Population	Treatment of <i>Helicobacter pylori</i> infection in adults.
Duration of Treatment	The recommended dosage regimen is vonoprazan 20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each given twice daily (morning and evening, 12 hours apart), with or without food, for 14 days.
Maximum Daily Dose	40 mg vonoprazan/2000 mg amoxicillin/1000 mg clarithromycin
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

This OPQ Assessment Addendum includes the Labeling Review and the Addendum to Drug Product Review, which addresses several issues related to drug product, pending at the time of the OPQ Assessment # 1. For other discipline reviews, including Drug Substance(s), Biopharmaceutics, and Manufacturing, refer to the OPQ Assessment # 1 (dated February 7, 2022, in DARRTS).

Drug Product: Adequate

The proposed drug product is a co-package containing vonoprazan tablets, amoxicillin capsules and clarithromycin tablets. Amoxicillin capsules and clarithromycin tablets used in the co-package are approved, commercially available drug products and LoAs to the respective ANDAs have been provided. The CMC information for vonoprazan tablets has been provided in NDA 215152.

Most of the drug product quality aspects were reviewed and covered in the Drug Product Review included in the OPQ Assessment # 1. However, several issues were listed as pending and they included: 1) (b) (4) risk assessment; 2) (b) (4) (statement of compliance); 3) drug product shelf-life; and 4) environmental assessment.

(b) (4) risk assessment

Vonoprazan contains a secondary amine, and, therefore, there is a risk for (b) (4) formation. The drug product manufacturing process includes (b) (4)

The (b) (4) risk assessment has been provided in the NDA. In response to FDA request, in the amendment dated February 17, 2022, the Applicant provided additional information regarding other potential (b) (4) sources, thus further confirming that the overall risk for (b) (4) formation in vonoprazan tablets is low based on the low daily dose (40 mg vonoprazan/day) and excipient levels, (b) (4)

(b) (4)

Drug product shelf-life

Although the stability data package submitted in the initial NDA included limited data for the proposed commercial package presentation, a significant amount of supportive stability data was submitted for individual components, and a (b) (4)-month shelf life was proposed by the Applicant for the triple and dual (proposed via NDA 215153) packs. During the NDA review, additional stability information was provided in several amendments. Based on the analysis of the overall stability data provided, (which included some unexplained fluctuating trends and inconsistencies for one of the vonoprazan impurities, related substance (b) (4) a shelf-life of 24 months has been granted for the triple and dual packs to be stored at room temperature. Additionally, a release acceptance criterion was added for vonoprazan related substance (b) (4) in the drug product specification to help to ensure that (b) (4) does not go out of specification before the 24-month expiry date *(for detailed discussion of stability data and the calculation of the expiration dating for triple and dual packs, refer to the Drug Product Review Addendum, below)*.

Environmental Assessment (EA)

Additional information regarding Environmental Assessment was requested by James Laurenson (EA Team) and submitted in the amendment dated January 31, 2022. Based on the overall information provided, the claim of categorical exclusion has been found acceptable.

For further details refer to the Drug Product Review Addendum, below.

Labeling: Adequate

The proposed prescribing information (PI), container label, and carton labeling were found to generally include the necessary information from the product quality perspective. Several revisions and additions have been recommended in the applicable to the product quality sections of the PI (Sections 3, 11 and 16); also, for the container/blister label and carton labeling. Labeling recommendations have been communicated and accepted by the Applicant. *For details, refer to the Labeling Review, below.*

Manufacturing: Adequate

The manufacturing process and all the manufacturing facilities were found acceptable by the Office of Pharmaceutical Manufacturing Assessment (OPMA). The Overall Manufacturing Inspection Recommendation (OMIR) of "Approve" was entered into Panorama on January 25, 2022 *(for details refer to the Manufacturing Integrated Assessment included in the OPQ Assessment # 1)*.

In addition, in the email to RBPM (dated April 28, 2022), Dr. Jiao Yang has confirmed that all facilities remain in adequate status at this time.

C. Risk Assessment (*vonoprazan tablets*)

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	Formulation Raw materials Process parameters Scale/equipment Site	Low	(b) (4)	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	

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CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing

Information: The prescribing information was updated in Seq. # 0041 to include the proposed OPQ changes. All OPQ recommendations were implemented. Additionally clarifying language was proposed by the applicant in Section 16.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

As submitted in Seq. #0002, dated September 3, 2021:



With OPQ recommended edits:

(b) (4) **TRIPLE PAK** (vonoprazan tablets; amoxicillin capsules; clarithromycin tablets), co-packaged for oral use and (b) (4) **DUAL PAK** (vonoprazan tablets; amoxicillin capsules), co-packaged for oral use

TRADENAME TRIPLE PAK: Carton of 14 daily administration packs for morning and evening dosing, each containing the following three drug products (0):

- Tablets: Vonoprazan 20 mg
- Tablets: Clarithromycin 500 mg
- Capsules: Amoxicillin 500 mg

TRADENAME DUAL PAK: Carton of 14 daily administration packs for morning, mid-day and evening dosing, each containing the following two drug products (**Error! Reference source not found.**):

- Tablets: Vonoprazan 20 mg

- Capsules: Amoxicillin 500 mg

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	Punctuation in drug product name list revised per Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry Consulted with and defer to OND team for order of drug products
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Remove language with # of tablets/capsules in each container. We deferred to the labeling team for the inclusion of the carton information as well dosing schedule information. It was suggested as this may help to emphasize the difference between the triple and dual pack in the Highlights and Section 3.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the	Adequate	Strength is based on the active moiety (listed appropriately in Section 11):

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		(b) (4) 20 mg of vonoprazan
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1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: <i>"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"</i>	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	Amoxicillin Capsules USP requirement: Labeling: When more than one <i>Dissolution</i> test is given, the labeling states the <i>Dissolution</i> test used only if <i>Test 1</i> is not used.

Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		In Section 11, the following statement is made: "Meets USP Dissolution Test 2."
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.^x"</i> with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

As submitted in Seq. #0002, dated September 3, 2021:



With OPQ recommended edits:

3.1 TRADENAME TRIPLE PAK

TRADENAME TRIPLE PAK is a co-package consisting of 14 administration packs for morning and evening dosing. Each administration pack contains the following three drug products:

- Vonoprazan Tablets, 20 mg: pale red, oval, film-coated tablets debossed V20 on one side and plain on the other side.
- Amoxicillin Capsules, 500 mg: yellow, opaque, hard gelatin capsules imprinted with AMOX 500 on one side and GG 849 on the other side.
- Clarithromycin Tablets, 500 mg: white, oval, film-coated debossed GG C9 on one side and plain on the other side.

3.2 TRADENAME DUAL PAK

TRADENAME DUAL PAK is a co-package consisting of 14 administration packs for morning, mid-day and evening dosing. Each administration pack contains the following two drug products:

- Vonoprazan Tablets, 20 mg: pale red, oval, film-coated tablets debossed V20 on one side and plain on the other side.
- Amoxicillin Capsules, 500 mg: yellow, opaque, hard gelatin capsules imprinted with AMOX 500 on one side and GG 849 on the other side.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	We deferred to the labeling team for the inclusion of the carton information as well dosing schedule information. It was suggested as this may help to emphasize the difference between the triple and dual pack in the Highlights and Section 3.
Strength(s) in metric system	Adequate	Remove comma before strength
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	Strength is based on the active moiety as described in Section 11: (b) (4) 20 mg of vonoprazan (b) (4) 500 mg amoxicillin (b) (4)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Remove "500 mg" from description of amoxicillin and clarithromycin Remove (b) (4) throughout label to reduce clutter
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate	Products not scored
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

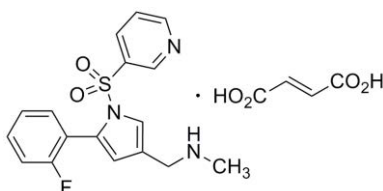
Section 11 (DESCRIPTION)

With OPQ recommended edits:

(b) (4) TRIPLE PAK contains vonoprazan 20 mg tablets, amoxicillin 500 mg capsules and clarithromycin 500 mg tablets for oral administration. (b) (4) DUAL PAK contains vonoprazan 20 mg tablets and amoxicillin 500 mg capsules, both for oral administration.

Vonoprazan Tablets

Vonoprazan is a potassium-competitive acid blocker (PCAB). Chemically, it is 1-*H*-Pyrrole-3-methanamine, 5-(2-fluorophenyl)-*N*-methyl-1-(3-pyridinylsulfonyl)-,2-butenedioate (1:1). Its empirical formula is $C_{17}H_{16}FN_3O_2S \cdot C_4H_4O_4$ with a molecular weight of 461.5. Vonoprazan has the following structure:

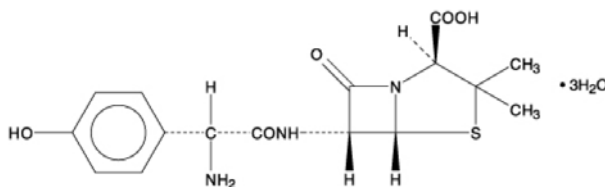


Vonoprazan fumarate is white to nearly white crystals or crystalline powder which melts at 194.8°C. Vonoprazan fumarate is soluble in dimethyl sulfoxide; sparingly soluble in *N,N*-dimethylacetamide, slightly soluble in *N,N*-dimethylformamide, methanol and water; very slightly soluble in ethanol (99.5);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

Each film-coated tablet contains 20 mg of vonoprazan, present as 26.72 mg of vonoprazan fumarate and the following inactive ingredients: croscarmellose sodium, ferric oxide red, fumaric acid, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

Amoxicillin Capsules

Amoxicillin is a penicillin class antibacterial, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically it is (2*S*, 5*R*, 6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid trihydrate. The molecular formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ and the molecular weight is 419.45. Amoxicillin has the following structure:

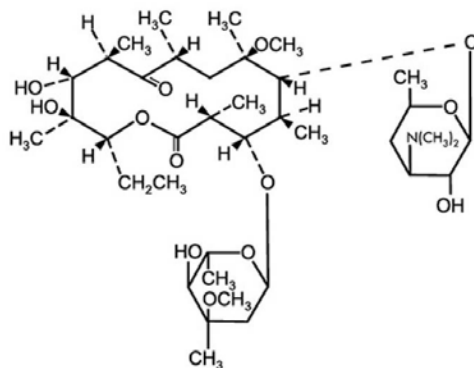


Each amoxicillin capsule, with yellow opaque cap and body, contains 500 mg amoxicillin as the trihydrate. Inactive ingredients: Capsule shells – ammonium hydroxide, black ferric oxide, gelatin, propylene glycol, potassium hydroxide, shellac, titanium dioxide and yellow ferric oxide; Capsule contents – cellulose microcrystalline and magnesium stearate.

Meets USP Dissolution Test 2.

Clarithromycin Tablets

Clarithromycin is a semi-synthetic macrolide antimicrobial for oral use. Chemically, it is 6-*O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. Clarithromycin has the following structure:



Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water.

Each clarithromycin tablet contains 500 mg of clarithromycin and the following inactive ingredients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, talc and titanium dioxide.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	Equivalency statement revised to list active moiety first: "Each film coated tablet contains 20 mg of vonoprazan, present as 26.72 mg of vonoprazan fumarate" Amoxicillin section states: "Each amoxicillin capsule, with yellow opaque cap and body, contains 500 mg amoxicillin as the trihydrate" which is acceptable as hydrate form is not a salt. The text as is matches the labeling text in ANDA 064076: ANDA064076 (064076 - 0038 - (115) - 2021-11-22 - ANRPT-26 /New/Annual Report) - Final Package Insert - Sandoz - 46271430 (#2)
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Revised to put inactive ingredients in alphabetical order per USP<1091>.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	

Chemical name, structural formula, molecular weight	Adequate	Chemical name and molecular weight for vonoprazan fumarate revised to match USAN file for vonoprazan fumarate. "O" (zero) change to O (letter) in clarithromycin chemical name From Karina, DS reviewer: For amoxicillin the label describes name, molecular formula and molecular weight but not appearance or solubility. While for Vonoprazan and clarithromycin the label includes appearance and solubility.
If radioactive, statement of important nuclear characteristics.	Adequate	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section	Adequate	

of the PI (e.g., Section 2).		
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1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

As submitted in Seq. #0002, dated September 3, 2021:



With OPQ recommended edits:

TRADENAME TRIPLE PAK is a co-package containing:

- Vonoprazan Tablets, 20 mg: pale red, oval, film-coated tablets debossed V20 on one side and plain on the other side.
- Amoxicillin Capsules, 500 mg: yellow, opaque, hard gelatin capsules imprinted with AMOX 500 on one side and GG 849 on the other side.
- Clarithromycin Tablets, 500 mg: white, oval, film-coated tablets debossed GG C9 on one side and plain on the other side.

Vonoprazan tablets, amoxicillin capsules and clarithromycin tablets are supplied in separate blister cavities within the same blister card.

Each carton (NDC 81520-255-14) contains 56 tablets and 56 capsules divided into 14 daily dose blister cards.

Each daily blister card ((b) (4)) contains two vonoprazan tablets (20 mg each), four amoxicillin capsules (500 mg each) and two clarithromycin tablets (500 mg each), and indicates which tablets and capsules need to be taken in the morning and evening.

Store between 20°C and 25°C (68°F and 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature). Protect from light.

TRADENAME DUAL PAK is a co-package containing:

- Vonoprazan Tablets, 20 mg: pale red, oval, film-coated tablets debossed V20 on one side and plain on the reverse side.
- Amoxicillin Capsules, 500 mg: yellow, opaque, hard gelatin capsules imprinted with AMOX 500 on one side and GG 849 on the other side.

Vonoprazan tablets and amoxicillin capsules are supplied in separate blister cavities within the same blister card.

Each carton (NDC 81520-250-14) contains 28 tablets and 84 capsules divided into 14 daily dose blister cards.

Each daily blister card ((b) (4)) contains two vonoprazan tablets (20 mg each) and six amoxicillin capsules (500 mg each) and indicates which tablets and capsules need to be taken in the morning, mid-day and evening.

Store between 20°C and 25°C (68°F and 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Revise and reformat section to reduce clutter and increase readability
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	Revise and reformat section to reduce clutter and increase readability Add total number of tablets & capsules in each pack. Following Prescribing Information recommendations, Phathom proposed to include "unit of use" to describe the carton to add clarity that each carton of the 14 daily dose blister cards is a saleable unit, which is acceptable from the product quality and DMEPA standpoint. Phathom also stated that the single daily blister card is not a saleable unit and has proposed to delete the NDC number for the individual blister card. Per DMEPA, removal of blister pack NDC from PI is acceptable given the intended use for the 14-day treatment cartons.
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Revise and reformat section to reduce clutter and increase readability
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate	Tablet is not scored

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Protect from light is added to triple pack storage statement, as clarithromycin label contains this statement. Protect from light is not added to dual pack storage statement as amoxicillin label does not contain this statement and no changes were observed in vonoprazan photostability studies.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

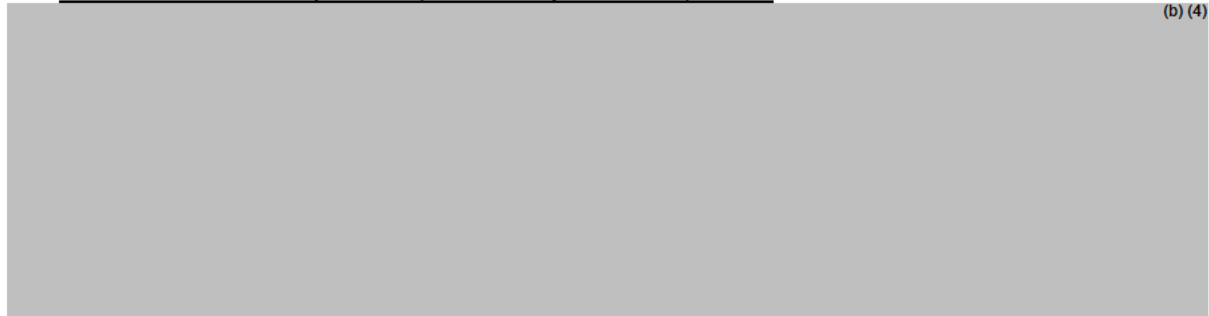
Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Revised to include: Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i>	N/A	
Include information about child-resistant packaging	Adequate	Testing was completed and compliance statement was

		provided in Module 3.2.P.7, but child-resistance is not stated in the label.
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1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

As submitted in Seq. #0002, dated September 3, 2021:



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

The carton and container labels were updated in Seq. # 0038 to include the proposed OPQ and DMEPA changes. All OPQ recommendations were implemented.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ² , (font size and prominence)	Adequate	Full Product Title, including dosage form for each component, must appear on label. Comment to applicant: Update the label to include the full product title, including dosage form and strength. For example, product title should be revised to read: "(b) (4) Triple Pak (Vonoprazan tablets; amoxicillin capsules; clarithromycin tablets)" Phathom submitted carton/container revisions with the following Product Title: VOQUEZNA TriplePak vonoprazan tablets 20 mg amoxicillin capsules 500 mg clarithromycin tablets 500 mg The following recommendation was sent: For the container labels and carton labeling of both the Triple Pak and Dual Pak, revise the established names to include a comma separating the established name from the strength. For example: VOQUEZNA TriplePak vonoprazan tablets, 20 mg amoxicillin capsules, 500 mg clarithromycin tablets, 500 mg

² Established name = [Drug] [Route of Administration] [Dosage Form]

Strength(s) in metric system	Adequate	Comment to applicant from DMEPA with proposed OPQ edits (omit USP): Update the label to indicate the strength per dosage unit. For example, revise to read: “2 vonoprazan tablets, 20 mg per tablet*” “4 amoxicillin capsules, 500 mg per capsule**” “2 clarithromycin tablets, 500 mg per tablet”
Route(s) of administration	Adequate	Added co-packaged for oral use to product title on carton
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	Adequate	Equivalency statements are present: *Each tablet contains 20 mg of vonoprazan (equivalent to 26.72 mg of vonoprazan fumarate). **Each capsule contains amoxicillin trihydrate (equivalent to 500 mg of amoxicillin).
Net contents (e.g., tablet count, volume of liquid)	Adequate	Net number of capsules/tablets were not present on carton label, but it does state: “14 Daily Treatment Packs” and “Each Daily Treatment Pack Contains...” OPQ comment to applicant: Update the label to include information on the net contents. For example, container label should include: “Carton contains 56 tablets and 56 capsules”
“Rx only” displayed on the principal display	Adequate	

NDC	Adequate	NDC number on blister pack matches with that proposed in (and removed from) the PI. Validation and verification of NDC #s is covered by the Office of Unapproved Drugs and Labeling Compliance. Comment to applicant from DMEPA: 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."
Lot number and expiration date	Adequate	Lot and expiration date were missing. Comment to applicant from DMEPA: 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 YYYYMM-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 humanreadable 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.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Revised to include: Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Linear bar code was absent. Comment to applicant from DMEPA: 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).

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Manufacturing information is listed on each tablet/capsule cavity backing. Manufacturing information is listed for each component on the carton label.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap over seal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	We recommended the removal of "(b) (4)" from the clarithromycin tablets and amoxicillin capsules product names throughout the label to reduce clutter and increase readability and clarity.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Adequate

Overall Assessment and Recommendation:

All OPQ recommendations were implemented in the prescribing information and carton/container labels.

Primary Drug Product Assessor Name and Date:

Molly Lee, Ph.D., Branch 2, ONDP Division of New Drug Products I, 4/27/2022

Secondary Assessor Name and Date:

Dorota Matecka, Ph.D., Branch 2, ONDP Division of New Drug Products I, 4/27/2022

Appears this way on original



Molly
Lee

Digitally signed by Molly Lee

Date: 4/27/2022 11:47:37PM

GUID: 5e2b04c70029e7c7580982b0a5cb16be



Dorota
Matecka

Digitally signed by Dorota Matecka

Date: 4/28/2022 07:51:11AM

GUID: 508173530000859092c69506374d0011

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/

DOROTA M MATECKA
05/02/2022 09:42:32 AM

RECOMMENDATION *Pending*

☐ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215152 Assessment # 1

Drug Product Name	(b) (4) Triple Pak* (vonoprazan tablets; amoxicillin capsules; clarithromycin tablets)
Dosage Form	Tablets and capsules
Strength	20 mg; 500 mg; 500 mg (<i>respectively</i>)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Phathom Pharmaceuticals, Inc.
US agent, if applicable	N/A

*Proposed trade name – under review

Submission(s) Assessed	Document Date	Discipline(s) Affected
0002	September 3, 2021	All
0012	December 17, 2021	Drug Substance, Drug Product, Process, Biopharmaceutics
0018	January 18, 2022	Drug Substance, Drug Product, Process
0020	January 24, 2022	Process
0021	January 25, 2022	Biopharmaceutics
0024	January 31, 2022	Environmental Assessment

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Karina Zuck	Katherine Windsor
Drug Product	Molly Lee	Dorota Matecka
Manufacturing	Jiao Yang	Steve Rhieu
Microbiology	Jiao Yang	Steve Rhieu
Biopharmaceutics	Min Kang	Elsbeth Chikhale
Environmental Analysis	James Laurenson (<i>refer to Drug Product Review</i>)	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs*:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	September 2, 2021	Review by Dr. Udofot
	II		(b) (4)	Adequate	October 19, 2021	Review by Dr. David Amspacher
	III		(b) (4)		N/A*	
	III		(b) (4)		N/A*	

*Sufficient information provided in the NDA – refer to the Drug Product Chapter

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
IND	143190	Development of triple therapy pack
ANDA	64076	Amoxicillin capsules used in the co-package (LoA provided in the NDA)
ANDA	65136	Clarithromycin tablets used in the co-package (LoA provided in the NDA)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	Adequate (acceptance criteria for impurities)	Refer to Drug Substance and Drug Product reviews	Dr. Leah Rosenfeld
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The majority of the CMC information provided in the NDA for all the drug substances and the drug product was found to be adequate. However, there are several outstanding issues that will need to be resolved, such as (b) (4) ; additional information regarding the (b) (4) risk assessment, and acceptability of the proposed expiration dating for the drug product. Also, the proposed labeling, including the package insert and the container and carton labels, are presently under review. The manufacturing and testing facilities have been found acceptable and the Overall Manufacturing Inspection Recommendation (OMIR) of "Approve" was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on January 25, 2022. However, due to the pending resolution of the remaining issues for the drug product, the final OPQ approvability recommendation for this NDA is currently **pending**.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

(b) (4) TRIPLE PAK, which has been developed for the treatment of *Helicobacter pylori* infection in adults, is a co-packaged combination product containing vonoprazan, a new potassium-competitive acid blocker (PCAB); amoxicillin, a penicillin class antibacterial; and clarithromycin, a macrolide antimicrobial.

The proposed commercial drug product (triple therapy pack) contains vonoprazan tablets, 20 mg, and previously approved, amoxicillin capsules, 500 mg, and clarithromycin tablets, 500 mg, all co-packaged in one blister card, on which each tablet or capsule is contained within its own blister cavity.

The proposed drug product combination received Fast Track (FT) and Qualified Infectious Disease Product (QIDP) designations on January 22, 2021 and May 16, 2021, respectively (for the treatment of *Helicobacter pylori* infection).

Proposed Indication(s) including Intended Patient Population	Treatment of <i>Helicobacter pylori</i> infection in adults.
Duration of Treatment	The recommended dose is vonoprazan 20 mg plus amoxicillin 1000 mg plus clarithromycin 500 mg, each taken twice daily, for 14 days (to be taken in the morning and evening with or without food).
Maximum Daily Dose	40 mg vonoprazan/2000 mg amoxicillin/1000 mg clarithromycin
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

*This NDA provides for a combination of three drugs (vonoprazan, amoxicillin, and clarithromycin) to be used for the treatment of *Helicobacter pylori* infection. The Applicant has concurrently submitted a second NDA (NDA 215153) for a combination of two drugs, vonoprazan and amoxicillin (dual therapy pack) for the same indication. These drug products have been developed in DAI via INDs 143190 and 144399, respectively. Amoxicillin and clarithromycin are known and approved antibacterial drugs, while vonoprazan is an NME*

(b) (4)

The drug product submitted in the current NDA (triple therapy pack) is a combination of vonoprazan tablets, 20 mg, and previously approved, amoxicillin capsules, 500 mg and clarithromycin tablets, 500 mg, all co-packaged in a blister card, on which each tablet or capsule is contained within its own blister cavity. The proposed commercial triple therapy blister card contains 2 vonoprazan tablets, 20 mg, 4 amoxicillin capsules, 500 mg, and 2 clarithromycin tablets, 500 mg. Each blister card contains the dosing regimen for one day. The proposed commercial packaging presentation includes 14 triple therapy blister cards packaged in a carton as a

(b) (4)

pack to cover the entire course of treatment (14 days).

The CMC information for amoxicillin capsules and clarithromycin tablets used in dual and triple therapy packs, has been provided via a reference to approved ANDAs 64076 and 665136, respectively. The CMC information for vonoprazan and vonoprazan tablets has been provided in NDA 215152.

Drug Substances: Adequate

Vonoprazan fumarate

Vonoprazan active ingredient used in the manufacture of the proposed drug product, vonoprazan tablets, is a fumaric acid salt. The entire supporting CMC information for vonoprazan fumarate drug substance was submitted in the NDA.

Vonoprazan fumarate is a white powder soluble in DMSO, sparingly soluble in N,N-dimethylacetamide, slightly soluble in methanol and water, and practically insoluble in acetone and acetonitrile. The intended commercial manufacturing process includes (b) (4)

Vonoprazan fumarate has been characterized by standard spectroscopic techniques (NMR spectroscopy, MS spectrometry, UV and IR spectroscopy, elemental analysis, and X-Ray diffractometry). The vonoprazan fumarate drug substance does not exhibit polymorphism and is controlled with appropriate tests and acceptance criteria included in the specification. The proposed acceptance criteria for impurities have been found qualified and an adequate overall adequate risk assessment for the elemental impurities (as per ICH Q3D) was provided. In addition, residual solvents are controlled in accordance with ICH Q3C.

The drug substance, vonoprazan fumarate, has been demonstrated to remain stable throughout (b) (4) storage conditions. Therefore, the proposed retest period of (b) (4) months has been granted for the drug substance to be stored at (b) (4) in the proposed commercial packaging.

Amoxicillin

The CMC information for amoxicillin drug substance is referenced to (b) (4) held by (b) (4). A letter of authorization (LoA) to (b) (4) and ANDA 64076 was provided in the NDA. (b) (4) was last reviewed on September 2, 2021 with reference to another application and was found adequate.

Amoxicillin (trihydrate) drug substance appears as a white or almost white crystalline powder. Amoxicillin is slightly soluble in water, methanol, ethanol and acetone, and practically insoluble in chloroform and diethyl ether. The Applicant provided in the NDA certificates of analysis (CoAs) for four amoxicillin drug substance batches used to manufacture three primary drug product stability batches and the data appear adequate.

Clarithromycin

The CMC information for clarithromycin drug substance is referenced to (b) (4) held by (b) (4). LoAs to (b) (4) and ANDA 65136 were provided in the NDA. (b) (4) was reviewed and found

adequate on October 19, 2021; no new quality amendments have been submitted since this latest review.

Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol and acetonitrile, and practically insoluble in water. The Applicant provided in the NDA CoAs for two clarithromycin drug substance batches used to manufacture three primary drug product stability batches and the data appear adequate.

Overall information provided all three drug substances in support of the proposed drug product, was found adequate by the Drug Substance Reviewer.

For further details refer to the Drug Substance Review, below.

Drug Product: Choose an item.

The proposed drug product is a co-package containing vonoprazan tablets, amoxicillin capsules and clarithromycin tablets. Amoxicillin capsules and clarithromycin tablets used in the co-package are approved, commercially available drug products and LoAs to the respective ANDAs have been provided. Therefore, the Drug Product review focused on the information provided in the NDA for vonoprazan tablets.

Amoxicillin capsules, 500 mg, to be used in the co-package, are manufactured by Sandoz GmbH (Austria) and approved via ANDA 64076. Similarly, clarithromycin tablets, 500 mg, to be included in the co-package, have been approved under ANDA 65136 and are manufactured by Sandoz S.R.L (Romania). The NDA does include a specification and batch release data for both, amoxicillin capsules and clarithromycin tablets. In addition, some stability data were provided in the NDA for each of these drug products in support of the proposed commercial drug product (a co-package).

Vonoprazan tablets

Vonoprazan tablet is an immediate release tablet formulated as pale red, oval, biconvex film coated tablets with V 20 debossed on one side and plain on the other side. Each tablet contains 26.7 mg of vonoprazan fumarate, equivalent to 20 mg vonoprazan, in addition to compendial excipients. The proposed commercial drug product manufacturer for vonoprazan tablets is (b) (4)

The drug product specification includes relevant quality attributes such as: appearance, identification, related substances, content uniformity, dissolution, assay and loss on drying.

Vonoprazan contains a secondary amine, and, therefore, there is a risk for (b) (4) formation. The drug product manufacturing process includes (b) (4)

Although the overall risk for (b) (4) presence is likely low (due to the low dose of vonoprazan, 40 mg/day and small quantities of excipients), a complete assessment on the maximum potential (b) (4) exposure including all possible (b) (4) sources should be provided. An IR will be sent to the applicant and the response will be evaluated in an addendum to this review.

The proposed drug product commercial container closure system is a (b) (4) blister with separate cavities for four tablets (two vonoprazan and two clarithromycin) and four amoxicillin capsules. Overall information provided for the container closure system was found acceptable by the Drug Product Reviewer; (b) (4)

In response to the Agency IR, the Applicant stated that the blister packs will be tested to confirm compliance prior to commercialization. A follow-up discussion with the Applicant is needed to better understand their plans for testing and providing this required statement to the NDA.

Although the stability data package submitted in the NDA includes limited data for the proposed commercial package presentation, a significant amount of supportive stability data was submitted for individual components, and a (b) (4)-month shelf life was proposed by the Applicant. There were no out of specification results reported in any of the studies; however, some unexplained fluctuating trends and inconsistencies were observed across the data, for example, for some of the vonoprazan impurities. Based on these observations, a shelf-life of 24 months was determined to be more reasonable for this product. The issue of the expiration dating will be discussed with the Applicant, and further addressed in an addendum to this review.

Additional information regarding Environmental Assessment was requested by James Laurenson (EA Team) and submitted on in the amendment dated January 31, 2022. Review of this information is currently pending and will be included in the addendum.

For further details refer to the Drug Product Review, below.

Labeling: Choose an item.

The proposed prescribing information (PI), container labels, and carton labeling were found to generally include the necessary information. Several revisions and additions have been recommended in the applicable to the product quality sections of the PI (Sections 3, 11 and 16); also, for the container/blister label and carton labeling. Labeling recommendations have been communicated to OND PM and are under discussion with DMEPA. The labeling review will be included in the addendum to the this review.

Manufacturing: Adequate

Manufacturing assessment focused on the review of all facilities and the manufacturing process for vonoprazan tablets since the two other components of the proposed triple therapy package are approved drug products (amoxicillin capsules and clarithromycin tablets).

Vonoprazan tablets were developed by Takeda Pharmaceutical Company Limited and first received approval as TAKECAB® in Japan (and subsequently approved in Asia and Latin America). The Applicant licensed the exclusive rights from Takeda to develop, manufacture, and commercialize vonoprazan tablets in the United States, Canada, and Europe. The Applicant did not conduct manufacturing process development study; instead, to support this NDA the Applicant refers to the manufacturing process development performed by Takeda. The selected manufacturing process is identical to the manufacturing process

(b) (4)

The process flow diagram was provided with every manufacturing step

(b) (4)

The overall information provided in the initial NDA submission and the subsequent amendments regarding the manufacturing process and controls for vonoprazan tablets have been found adequate by the Process Reviewer.

The commercial manufacturing of vonoprazan drug substance will be conducted at (b) (4), which is a known commercial manufacturer of active pharmaceutical ingredients. Vonoprazan tablets for commercial use will be manufactured by (b) (4)

(b) (4), which is a known manufacturer of solid dosage forms and has an acceptable profile of TCM. All other facilities listed in the NDA involved in the manufacture of the two other drug substances (amoxicillin and clarithromycin), and the two other drug products (amoxicillin capsules and clarithromycin tablets) have been also evaluated and found to be GMP compliant. This includes (b) (4), which is the proposed commercial packager of the three drug products into blister (b) (4) packs.

All manufacturing facilities have been found acceptable by OPMA based on the review of their previous inspectional history. The overall "Approve" recommendation for manufacturing facilities was entered into Panorama on January 25, 2022 (for details refer to the Manufacturing Integrated Assessment, below).

Comparability Protocol

(b) (4)

Several recommendations were conveyed to the Applicant from the review team that also included input from OLDP (Dr. Rishi Thakur). The revised protocol was resubmitted in the amendment dated January 18, 2022 and found acceptable by the review team (refer to the Drug Substance Review and Manufacturing Integrated Assessment, below).

Biopharmaceutics: Adequate

The Biopharmaceutics review focused on the evaluation of (1) the in vitro dissolution data and the acceptance criterion for the proposed drug product, and (2) the bridging between [i] different formulations of vonoprazan tablets, [ii] over-encapsulated vonoprazan tablets and un-encapsulated vonoprazan tablets, and [iii] vonoprazan tablets manufactured at two different sites having two different images (e.g., (b) (4) tablets with strength printed vs. (b) (4) tablets with strength debossed).

Dissolution:

The following in vitro dissolution methods and dissolution acceptance criteria shown in the table below are found acceptable for batch release and stability testing:

Drug Product	Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
Vonoprazan ¹ Tablets	USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.05 M Acetate Buffer (pH 4.5)	$Q = \frac{(b)(4)}{(4)}\%$ at 15 minutes
Amoxicillin ² Capsules	USP I (Basket)	100 rpm	900 mL/ 37 °C	Water	$Q = \frac{(b)(4)}{(4)}\%$ in 90 minutes

¹ The QC dissolution method for Vonoprazan Tablets had been approved during the IND stage. The approved Dissolution Method Development Report can be found at the following link (applicable for (b) (4) IND 144399, IND 143190):

<https://darts.fda.gov/darts/ViewDocument?documentId=090140af8061ece7>

² The QC dissolution method for Amoxicillin Capsules had been evaluated and approved as part of the ANDA 064076 (Sandoz)

Clarithromycin ³ Tablets	USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.1 M Sodium Acetate Buffer (pH 5.0)	$Q = \frac{(b)(4)}{(4)}\%$ in 30 minutes
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Bridging:

Vonoprazan Tablets:

During development of vonoprazan tablets, 20 mg, formulations T2, T3, and T4 were used. The bridge between formulations/batches studied in the clinical trials and the proposed commercial drug product have been evaluated and determined to be adequately bridged via in vitro dissolution data for the following: (1) formulations T2, T3, and T4, (2) over-encapsulated tablet to un-encapsulated tablet, (3) drug product manufacturing sites, and (4) tablet Image.

Clarithromycin Tablets:

Commercially available generic clarithromycin tablets (ANDA 65489, Aurobindo Pharma Limited) were used in the Pivotal Study (HP-301); however, other commercially available generic clarithromycin tablets (ANDA 65136, Sandoz GmbH) are being proposed for the commercial (b) (4) Triple Therapy (b) (4) packs. Given the proven bioequivalence of the generic drug products to the RS (ANDA 65489), additional bridging is not needed.

Amoxicillin Capsules:

The same commercially available generic amoxicillin capsules (ANDA 64076, Sandoz GmbH) that were used in the Pivotal Study (HP-301) are being proposed for the commercial drug product (triple therapy packs). Therefore, bridging is not needed.

The overall Biopharmaceutics information submitted in the NDA was found adequate by the Biopharmaceutics Reviewer. For further details refer to the Biopharmaceutics Review, below.

Microbiology: Adequate

The proposed drug product is a co-package of three drug products, oral solid dosage forms. Therefore, a separate microbiology review was not needed. The microbiological controls proposed for the finished commercial drug product were found adequate by the Process Reviewer (refer to the Manufacturing Integrated Assessment, below).

C. List of Pending Issues

Drug Product:

The following issues are currently pending/are under discussion and will be addressed in the addendum to this review:

1. (b) (4) proposed commercial container closure system
2. Additional information regarding the (b) (4) risk assessment
3. Drug product expiration dating
4. Environmental assessment
5. Labeling

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NDA/ Type of Submission: NDA 215152-ORIG-1; 505(b)(2)
Applicant Name: Phathom Pharmaceuticals Inc
Drug Product Name & Strength: (b) (4) Triple Pak (Vonoprazan Tablets 20 mg, Clarithromycin Tablets (b) (4) 500 mg, and Amoxicillin Capsules (b) (4) 500 mg)
Route of Administration: Oral
Submission Date: 09/03/2021 (Original Submission)
Primary Biopharmaceutics Reviewer: Min (Sammie) Kang, Pharm.D., M.S.
Secondary Biopharmaceutics Reviewer: Elsbeth Chikhale, Ph.D.

BACKGROUND AND SUMMARY

The Applicant submitted this 505(b)(2) NDA seeking approval for (b) (4) Triple Pak (Vonoprazan Tablets 20 mg, Clarithromycin Tablets (b) (4) 500 mg, and Amoxicillin Capsules (b) (4) 500 mg). Vonoprazan belongs to a new class of acid-inhibitory agents called potassium-competitive acid blocker (PCAB). The current NDA submission has been granted Qualified Infectious Disease Product (QIDP) designation (5-5-2021) and Fast Track designation on (1-22-2021). The proposed drug product (co-packaged triple pack) is indicated for the treatment of *Helicobacter pylori* (*H pylori*) infection. The proposed dose is Vonoprazan 20 mg BID (twice daily), Amoxicillin 1000 mg BID (twice daily), and Clarithromycin 500 mg BID (twice daily) for 14 days. This application is primarily supported by clinical safety and efficacy data obtained from two Pivotal Clinical Phase 3 Studies (HP-301 and TAK-438/CCT-401), and relies in part on FDA's previous findings of safety and efficacy for the two co-packaged approved generic drug products, Amoxicillin Capsules and Clarithromycin Tablets.

This Biopharmaceutics Review focuses on the evaluation of (1) the in vitro dissolution data and the acceptance criterion as a quality control (QC) for the proposed drug product, and (2) the bridging between [i] different formulations of vonoprazan tablets, [ii] over-encapsulated vonoprazan tablets and un-encapsulated vonoprazan tablets and [iii] vonoprazan tablets manufactured at two different sites having two different images (e.g., (b) (4) tablets with strength printed vs. (b) (4) tablets with strength debossed).

In Vitro Dissolution Methods and Acceptance Criteria: ACCEPTABLE

The following in vitro dissolution methods and dissolution acceptance criteria shown in the table below are found acceptable for the Quality Control (QC) testing of (b) (4) Triple Pak (Vonoprazan Tablets 20 mg, Clarithromycin Tablets (b) (4) 500 mg, and Amoxicillin Capsules (b) (4) 500 mg), for batch release and stability testing:

Drug Product	Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
Vonoprazan ¹ Tablets	USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.05 M Acetate Buffer (pH 4.5)	Q = (b) (4) % at 15 minutes
Amoxicillin ² Capsules	USP I (Basket)	100 rpm	900 mL/ 37 °C	Water	Q = (b) (4) % in 90 minutes

¹ The QC dissolution method for Vonoprazan Tablets had been approved during the IND stage. The approved Dissolution Method Development Report can be found at the following link (applicable for (b) (4) IND 144399, IND 143190):
<https://darts.fda.gov/darts/ViewDocument?documentId=090140af8061ece7>

² The QC dissolution method for Amoxicillin Capsules had been evaluated and approved as part of the ANDA 064076 (Sandoz)

Clarithromycin³ Tablets	USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.1 M Sodium Acetate Buffer (pH 5.0)	Q = (b) (4) % in 30 minutes
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Biowaiver Request: NOT APPLICABLE

The Applicant submitted a BCS-based biowaiver request⁴ to support the formulation changes to the vonoprazan tablet during clinical development (T1 to T4). However, the formulation changes (b) (4) between the T1 and T2, T2 and T3, and T3 and T4 formulations are deemed minor (e.g., within ±10%) and can be bridged by dissolution profile comparison if needed. Therefore, a bioequivalence study will not be necessary (i.e., the BCS-based biowaiver is not required to bridge formulations T1 to T4).

Bridging: ACCEPTABLE

Vonoprazan Tablets: During the drug development of Vonoprazan Tablets, 20 mg, formulations T2, T3, and T4 were used. The bridge between formulations/batches studied in the clinical trials and the proposed commercial drug product have been evaluated and was determined to be adequately bridged via in vitro dissolution data for the following: (1) Formulations T2, T3, and T4, (2) Over-encapsulated Tablet to Un-encapsulated Tablet, (3) Drug Product Manufacturing sites, and (4) Tablet Image. Please reference Section 7 of the review for the details.

Clarithromycin Tablets: Commercially available generic clarithromycin tablets (ANDA 065489, Aurobindo Pharma Limited) were used in the Pivotal Study (HP-301); however, other commercially available generic clarithromycin tablets (ANDA 055136, Sandoz GmbH) are being proposed for the commercial (b) (4) Triple Therapy (b) (4) packs. Given the proven bioequivalence of the two generic drug products to the RS⁵ (ANDA 065489), additional bridging is not needed.

Amoxicillin Capsules: The same commercially available generic amoxicillin capsules (ANDA 064076, Sandoz GmbH) that were used in the Pivotal Study (HP-301) are being proposed for the commercial (b) (4) Triple Therapy (b) (4) packs. Therefore, bridging is not needed.

Overall Recommendation: From the Biopharmaceutics perspective, NDA 215152 for the proposed (b) (4) Triple Pak (Vonoprazan Tablets 20 mg, Clarithromycin Tablets (b) (4) 500 mg, and Amoxicillin Capsules (b) (4) 500 mg), is **Adequate** and recommended for Approval.

³ The QC dissolution method for Clarithromycin Tablets had been evaluated and approved as part of the ANDA 065136 (Sandoz)

⁴ [NDA215152 \(215152 - 0015 - \(15\) - 2022-01-03 - ORIG-1 /Clinical/Response To Information Request\) - Request for Waiver for in vivo Studies](#)

⁵ RLD (NDA 050662) is currently discontinued

BIOPHARMACEUTICS ASSESSMENT**1. List of Submissions Reviewed:**

SDN	Received date	Document
2	09/03/2021	Original NDA submission
12	12/17/2021	Quality/Response to Quality/Biopharmaceutics IR #1
18	01/18/2022	Quality/Response to Biopharmaceutics IR #1

2. BCS Designation:

Solubility of Vonoprazan: The vonoprazan fumarate drug substance is considered highly soluble per the BCS classification as evidenced by its high solubility (> 0.08 mg/mL [20 mg/250 mL]) across the physiologic pH (pH 1-7), as described below in Table 1.

Table 1: Solubility vs. pH at 37 °C

Test buffer	Solubility as TAK-438F in Test Buffer	
	Average [mg/mL]	RSD [%]
pH 1.2	19.9	0.3
pH 3.6	4.83	0.6
pH 4.5	5.02	0.6
pH 5.6	4.64	1.9
pH 6.8	4.62	2.6

Permeability of Vonoprazan: The Applicant has submitted the permeability data⁶ of vonoprazan based on in vitro intestinal permeability study using Caco-2 cell monolayers. (b) (4)

Dissolution of Vonoprazan: The in vitro dissolution profile of Vonoprazan Tablets (20 mg) in multi-pH (b) (4) show a very rapid dissolution ($\geq$ (b) (4) % dissolution within 15 minutes).

Reviewer's comments: Based on the above information, Vonoprazan may be classified as highly soluble. (b) (4)
The BCS (b) (4) designation is not needed for the approval of this NDA, since a BCS-based biowaiver is not needed for the approval of this NDA.

⁶ (b) (4)

⁷ (b) (4)

(b) (4)

For the solubility of Amoxicillin and Clarithromycin drug substances, ANDA 064076 and ANDA 065136 should be referenced, respectively

3. Formulation Composition:

Table 2 shows the formulation composition of the Vonoprazan Tablets, 20 mg (T2, T3, and T4) used during the drug product development.

Table 2: Composition of Formulation T2

Table 3: Composition of Formulation T3

(b) (4)

Table 4: Composition of Formulation T4 (final proposed formulation)

Component	Function	(b) (4) 20 mg tablet (mg)
Vonoprazan fumarate		26.72
(Vonoprazan)	Active	(20)
(b) (4) (4)mannitol		(b) (4)
Microcrystalline cellulose ^a		
Hydroxypropyl cellulose		
Fumaric acid		
Croscarmellose sodium		
Magnesium stearate		
Hypromellose ^b		
(b) (4)		
Titanium dioxide		
Red ferric oxide		
(b) (4)		
Total		

Parentheses indicate content in terms of the free base of vonoprazan (salt conversion factor: 1.336).
Unit: mg/tablet

(b) (4)

(b) (4)
The drug product manufacturing process for the final proposed immediate-release oral Vonoprazan Tablets, 20 mg, include: (b) (4)
(b) (4). For the formulation composition information and manufacturing process of Amoxicillin Capsules and Clarithromycin Tablets, refer to ANDA 064076 and ANDA 065136, respectively.

4. Dissolution Method Development:

Vonoprazan Tablets: The proposed QC dissolution method for the proposed Vonoprazan Tablets, 20 mg, had been found acceptable as part of the IND submissions (b) (4) IND 144399 [SDN-23], IND 143190 [SDN-31]). The review of the complete Dissolution Method Development Report can be found at the following link (finalized on 10-19-2021):

<https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af8061ece7>

Amoxicillin Capsules: The proposed QC dissolution method for Amoxicillin Capsules 500 mg has been evaluated and approved as part of the ANDA 064076 (Sandoz)

Clarithromycin Tablets: The proposed QC dissolution method for Clarithromycin Tablets 500 mg has been evaluated and approved as part of the ANDA 065136 (Sandoz)

The following proposed QC dissolution methods are found acceptable:

Drug Product	Apparatus	Speed	Volume/ Temp	Medium
Vonoprazan Tablets	USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.05 M Acetate Buffer (pH 4.5)
Amoxicillin Capsules	USP I (Basket)	100 rpm	900 mL/ 37 °C	Water
Clarithromycin Tablets	USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.1 M Sodium Acetate Buffer (pH 5.0)

5. Dissolution Data and Acceptance Criterion:

The Applicant's registration stability lots for the Proposed Triple (b) (4) Pack Blister Card are described below in Table 3.

Table 3: The Registration Lots for the Proposed Triple (b) (4) Pack Blister Card

Manufacturer	(b) (4)		Amoxicillin Capsules 500 mg	Clarithromycin Tablets 500 mg
			(b) (4) Sandoz GmbH (Kundl, Austria)	Sandoz S.R.L. (Targu Mures, Romania)
Lot 1	32066685	11920534	KZ8535	KZ2349
Lot 2	32066688	11921111	KZ8536	KZ2349
Lot 3	32066690	11921112	KZ8538	KZ2349

1—Vonoprazan Tablets: The in vitro dissolution profiles of the clinical lots for the Vonoprazan Tablets, 20 mg (Study HP-301, formulation T4, Bulk Lot# H1223 [PCI Kit ID#: 504716, 500317, 504592]⁸) shows a very rapid dissolution ($\geq$ (b) (4) % dissolution within 15 minutes) using the proposed QC dissolution method as shown in Table 4 below.

Table 4: Dissolution Profile of the Clinical Lot of Vonoprazan Tablets, 20 mg (H1223)

Media	Sample	10 min	15 min	30 min	45 min
pH 4.5 (20 mg)	Blinded	(b) (4)			
	504716				
	Blinded				
	500317				
	Blinded				
	504592				

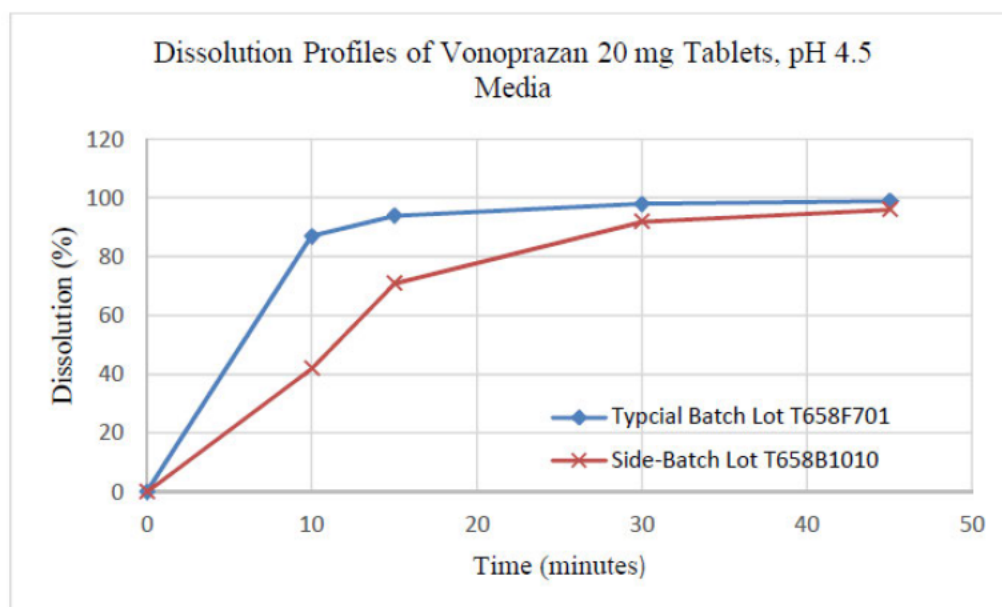
The formulation used in clinical study TAK-438/CCT-401 was formulation T3 and it also shows a very rapid dissolution ($\geq$ (b) (4) % dissolution within 15 minutes) in multi-pH media (USP Apparatus II, in 900 mL at 50 rpm; (b) (4)); please reference Figure 2 under Section 7. Also, the proposed registration batches ((b) (4) lot # 11888539 and (b) (4) Lot#: 4435098) show a very rapid dissolution ($\geq$ (b) (4) % dissolution within 15 minutes) using the proposed QC dissolution method; please reference Table 7 and Figure 4 under Section 7. The Applicant has initially proposed a dissolution acceptance criterion of “(b) (4)” however, based on the submitted in vitro dissolution profile in the current submission (Table 4 and 7) along with the in vitro dissolution data submitted to support the discriminating ability (Table 5 and Figure 1 below; submitted as part of the Dissolution Method Development Report dated 6-10-20 in the (b) (4) IND-143190, IND-144399) which showed that the dissolution method is capable of discriminating against the aberrant/ side batch (T658B101) if a dissolution criterion of $Q = (b) (4) \%$ at 15 minutes is set, the Applicant was requested to tighten the dissolution acceptance criterion to “ $Q = (b) (4) \%$ in 15 minutes” via the Information Request dated 12-03-2021. In the Response dated 12-17-2021, the Applicant has agreed to FDA’s recommendation ($Q = (b) (4) \%$ at 15 minutes) and has updated relevant sections, M.3.2.P.5.1. and M.3.2.P.8.2., accordingly.

Table 5: Summary of Side batch information vs Typical/ Target batch

Tablet Strength	Lot No.	(b) (4)	Notes
20 mg	T658F701		Typical batch
	T658B101		Side batch

⁸ [NDA215152 \(215152 - 0018 - \(18\) - 2022-01-18 - ORIG-1 /Quality/Response To Information Request\) - Pharm Dev - Formulation Development - Original - \(b\) \(4\)-0001667 \(#39\)](#)

Figure 1: Dissolution Profiles of Typical Batch (Lot T658F701) and Side Batch (Lot T658B101) for Vonoprazan (b) (4) Tablets (20 mg), using the proposed method (Paddle Apparatus, 50 rpm, 0.05 mol/L Acetate Buffer Solution (pH 4.5) (n=6 tablets each))



2—Amoxicillin Capsules: The in vitro dissolution data of the registration lots for the Amoxicillin Capsules, 500 mg (proposed to be co-packaged in the Triple (b) (4) Pack Blister Card) adequately meets the dissolution acceptance criterion that has been evaluated and approved as part of the ANDA 064076 (Sandoz), “Q= (b) (4) % at 90 minutes”.

3—Clarithromycin Tablets: The in vitro dissolution data of the registration lots for the Clarithromycin Tablets, 500 mg (proposed to be co-packaged in the Triple (b) (4) Pack Blister Card) adequately meets the dissolution acceptance criterion that has been evaluated and approved as part of the ANDA ANDA 065136 (Sandoz), “Q= (b) (4) % at 30 minutes”.

Reviewer’s Comments: The in vitro dissolution data of the clinical and registration batches of Vonoprazan Tablets, Amoxicillin Capsules, and Clarithromycin Tablets, support the revised (vonoprazan) and proposed (amoxicillin and clarithromycin) dissolution acceptance criteria.

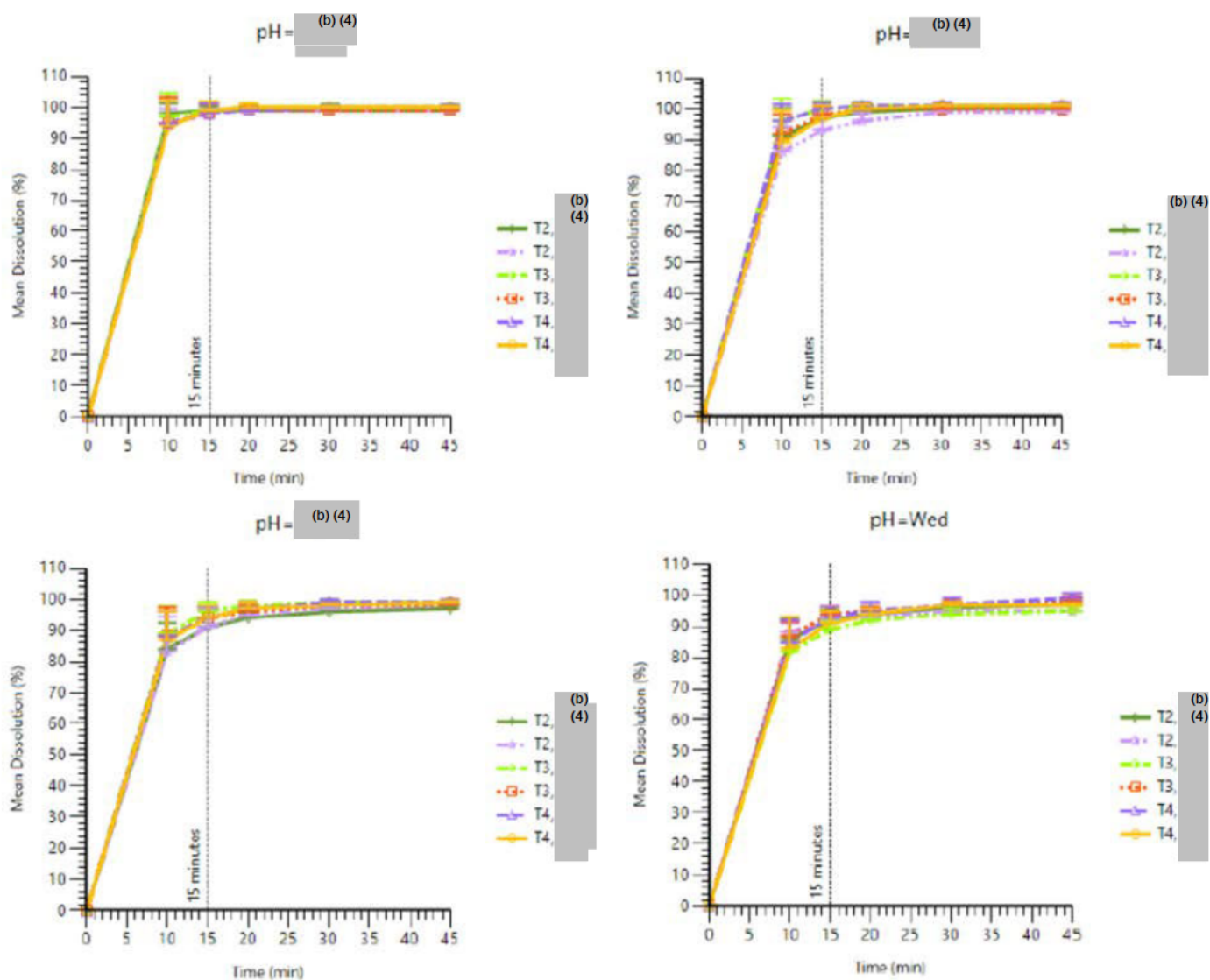
6. Dissolution Stability Data:

No significant trend in the dissolution on stability was observed with the Vonoprazan Tablets, Amoxicillin Capsules, and Clarithromycin Tablets packaged in the “(b) (4) Pack Blister Card” and stored for 6-month at accelerated condition ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\%\text{RH} \pm 5\%\text{RH}$), 12-month at intermediate condition ($4=30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\%\text{RH} \pm 5\%\text{RH}$), and 24-months at long-term stability study condition ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\%\text{RH} \pm 5\%\text{RH}$). All stability dissolution results met the proposed dissolution specifications.

7. Bridging:

1—Vonoprazan Tablets: During the drug development of Vonoprazan Tablets, 20 mg, formulations T1⁹, T2, T3, and T4 were used (See Table 2-4, Figure 2). The bridge between formulations/batches studied in the clinical trials and the proposed commercial drug product have been evaluated for the following: (1) Formulations T2, T3, and T4, (2) Over-encapsulated Tablet to Un-encapsulated Tablet, (3) Different drug product manufacturing sites, (4) different tablet image; see Figure 2 and Table 6, below.

Figure 2: Comparative dissolution of Formulations T2, T3, and T4, in Multi-pH (using USP Apparatus II, 900 mL at 50 rpm)



Abbreviations: Wed = Water (Japanese Pharmacopoeia 16th Edition Purified Water)

Table 6: Bridging of Vonoprazan Tablets, 20 mg

Vonoprazan Tablets, 20 mg		
	Drug products used in the Pivotal Study (HP-301) Drug Products Manufacturing Site: (b) (4) ¹⁰	
Encapsulation	Over-encapsulated (OE) T4 Tablets <u>Bulk Lot#: H1223</u>	Un-encapsulated (UE) T4 Tablets <u>Bulk Lot#: H1223</u> [PCI Kit ID#: 504716, 500317, 504592] ¹¹

Vonoprazan Tablets, 20 mg Co-packaged in Triple (b) (4)		
Bulk Tablet Manufacturing Site/ Tablet Image	Clinical drug product manufacturing site:	Proposed commercial drug product manufacturing site:
	(b) (4)	
	<i>with strength information 'printed' on the tablets</i>	<i>with strength information 'debossed V20' on the tablets</i>
	<u>Stability Lots#:</u> <u>11888539, 11888535, 11888583</u> ¹³ <u>Registration Stability Studies Lot#:</u> <u>11920534, 11921111, 11921112</u>	<u>Registration Stability/ Lot#:</u> <u>4435098</u> ¹⁴

First, there are two versions of vonoprazan drug product used in the Pivotal Study (HP-301): Over-encapsulated (OE) T4 Tablets which has been used to blind patients enrolled in the clinical study, versus the Un-encapsulated (UE) T4 Tablets which has been used as the control (unblind patients) in the clinical study (as described in Table 6 above). In order to appropriately bridge the two drug products, FDA had requested an in vitro dissolution study of the two T4 drug products (OE and UE) at different pH media (e.g., pHs (b) (4)) as part of the communications in the IND (b) (4)/143190/144399—Type A CMC Meeting Request dated 3-19-21. The Applicant provided in vitro dissolution data for Pivotal Study Bulk Lot#: H1223 and compared the OE-T4 Tablets to UE-T4 Tablets using the proposed QC dissolution method i.e., USP

¹⁰ Note that < (b) (4) > for the Clinical Formulations (e.g., T3 and T4 formulations) used in clinical studies other than the Pivotal Study [HP-301]: [NDA215152 \(215152 - 0016 - \(16\) - 2022-01-11 - ORIG-1 /Multiple Categories/Subcategories\) - Batch Analysis - Tablets - \(b\) \(4\) - Original - \(b\) \(4\)-0001609 \(#3\)](#)

¹¹ [NDA215152 \(215152 - 0018 - \(18\) - 2022-01-18 - ORIG-1 /Quality/Response To Information Request\) - Pharm Dev - Formulation Development - Original - \(b\) \(4\)-0001667 \(#39\)](#)

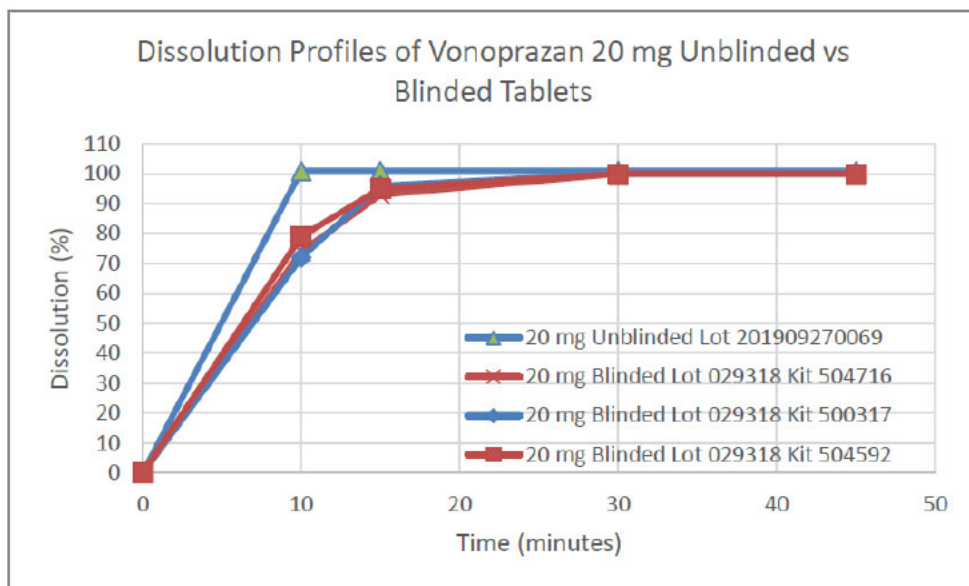
¹² Note that < (b) (4) > was also used to manufacture Commercial Scale Stability Lots ((b) (4))

¹³ [NDA215152 \(215152 - 0016 - \(16\) - 2022-01-11 - ORIG-1 /Multiple Categories/Subcategories\) - Batch Analysis - Tablets - \(b\) \(4\) - Original - \(b\) \(4\)-0001609 \(#17\)](#)

¹⁴ [NDA215152 \(215152 - 0016 - \(16\) - 2022-01-11 - ORIG-1 /Multiple Categories/Subcategories\) - Batch Analysis - Tablets - \(b\) \(4\) - Original - \(b\) \(4\)-0001610 \(#2\)](#)

Apparatus II [Paddle], 900 mL in pH 4.5 Acetate Buffer at 50 rpm (see General Advice Letter dated 6-2-20 of (b) (4), IND-143190 [SDN-31], IND-144399 [SDN-23]) showing very rapid dissolution for both OE and UE vonoprazan tablets, 20 mg ($\geq$ (b) (4) % in 15 minutes; see Figures 3 below) indicating similarity.

Figure 3: Comparative Dissolution Profiles for Unblinded (Un-encapsulated) and Blinded (Over-encapsulated) Vonoprazan Tablets, 20 mg (using the proposed QC dissolution method)

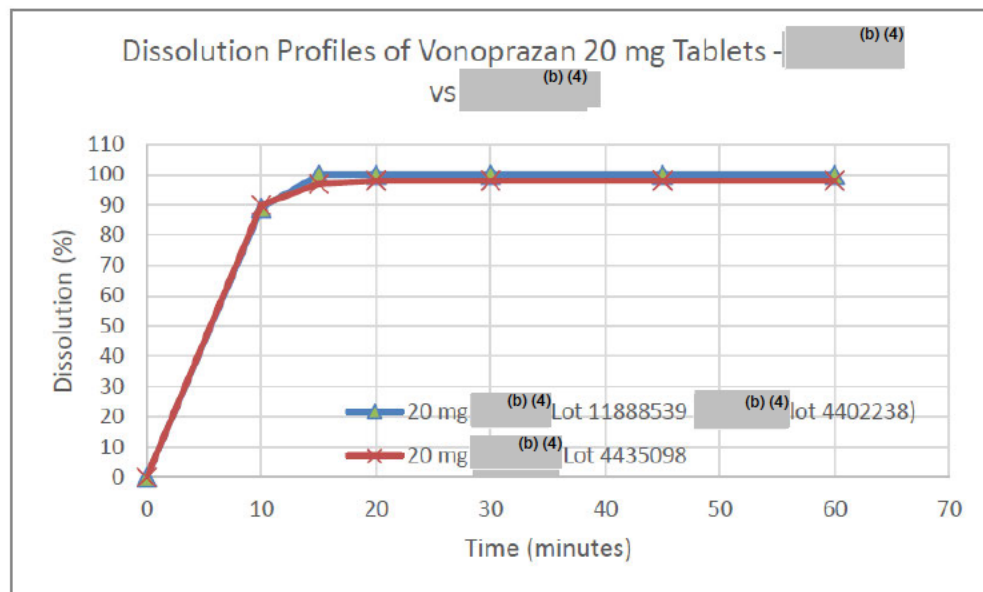


Secondly, the dissolution profiles of tablets manufactured at the (b) (4) site, with printing, were compared to the dissolution profiles of tablets manufactured at the (b) (4) site, which were debossed, using the proposed QC dissolution method which again showed a very rapid dissolution ($\geq$ (b) (4) % in 15 minutes; see Table 17 and Figures 4 below) indicating similarity.

Table 7: Summary of Comparative Dissolution Profile Results for (b) (4) (printed) and (b) (4) (debossed) Tablets, (b) (4) 20 mg, obtained using the proposed dissolution method.

Media	Sample	10 min	15 min	20 min	30 min	45 min	60 min
pH 4.5 (20 mg)	(b) (4)						
	(b) (4)						

Figure 4: Comparative Dissolution Profiles for Vonoprazan Tablets, 20 mg (b) (4) [strength printed] vs (b) (4) [strength debossed]) obtained using the proposed dissolution method



2—Clarithromycin Tablets: Based on the known bioequivalence of the Clarithromycin Tablets used in the pivotal clinical study (ANDA 065489) as well as the proposed commercial Clarithromycin Tablets (ANDA 055136) to the RLD, no additional bridging was necessary between the Clarithromycin Tablets used in the pivotal study (ANDA 065489 by Aurobindo Pharma Limited) and the proposed commercial and the proposed commercial Clarithromycin Tablets (ANDA 055136 by Sandoz GmbH); see Table 8 below.

3—Amoxicillin Capsules: No bridging between Amoxicillin Capsules was necessary because the same generic Amoxicillin Capsules used in the pivotal clinical studies (ANDA 064076, Sandoz GmbH) are being proposed as part of the commercial (b) (4) Triple Therapy (b) (4) packs; see Table 8 below.

Table 8: Comparison of Amoxicillin Capsules and Clarithromycin Tablets used in HP-301 versus Commercial Triple Therapy (b) (4) Pack – bridging evaluation is not applicable

	Drug products used in the Pivotal Study (HP-301)		To-be-marketed Commercial drug products
Amoxicillin Capsules, 500 mg	ANDA 064076, Sandoz GmbH	ANDA 064076, Sandoz GmbH	ANDA 064076, Sandoz GmbH
Clarithromycin Tablets, 500 mg	ANDA 065489, Aurobindo Pharma Limited	ANDA 065489, Aurobindo Pharma Limited	ANDA 065136, Sandoz GmbH

Reviewer's comments: From the Biopharmaceutics standpoint, as described above, the provided dissolution data for Vonoprazan Tablets, 20 mg, support the bridge between the batches studied in the pivotal clinical trials to the proposed commercial vonoprazan tablets, since all comparative dissolution profiles exhibit $> \frac{(b)}{(4)}\%$ dissolved in 15 minutes, thus indicating similarity.

No additional bridging is needed for the Clarithromycin Tablets and the Amoxicillin Capsules.

8. Compatibility Protocol: ADEQUATE

The Applicant has submitted a Compatibility Protocol (b) (4) FDA requested, via an Information Request dated 01-13-22, that the Applicant modify the comparability protocol, to include the plan to submit a complete dissolution profile for one exhibit drug product batch manufactured using vonoprazan fumarate from (b) (4) (b) (4). In the response dated 01-18-22¹⁵, the Applicant agreed to provide the requested dissolution profile (b) (4) along with the other test results and modified the comparability protocol accordingly. The Applicant's response is acceptable.

9. Biowaiver Request: NOT APPLICABLE

The Applicant submitted a BCS-based biowaiver request¹⁶ to support the formulation changes to the vonoprazan tablet during clinical development (T1 to T4). However, the formulation changes (b) (4) between the T1 and T2, T2 and T3, and T3 and T4 formulations are deemed minor (e.g., within $\pm 10\%$) and can be bridged by dissolution profile comparison if needed. Therefore, a bioequivalence study will not be necessary (i.e., the BCS-based biowaiver is not required to bridge formulations T1 to T4).

¹⁵ [NDA215152 \(215152 - 0018 - \(18\) - 2022-01-18 - TRIAGE-1 /Electronic Submission/Gateway\) - 2022-01-18 Response to 2022-01-13 FDA CMC Information Request NDA 215152 \(#15\)](#)

¹⁶ [NDA215152 \(215152 - 0015 - \(15\) - 2022-01-03 - ORIG-1 /Clinical/Response To Information Request\) - Request for Waiver for in vivo Studies](#)



Min (Sammie)
Kang

Digitally signed by Min (Sammie) Kang
Date: 1/24/2022 03:57:15PM
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Elsbeth
Chikhale

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Date: 1/24/2022 05:54:06PM
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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/

DOROTA M MATECKA
02/07/2022 10:27:27 PM

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215153

Assessment # 1 - Addendum

Drug Product Name	VOQUEZNA Dual Pak* (vonoprazan tablets; amoxicillin capsules)
Dosage Form	Tablets and capsules
Strength	20 mg; 500 mg (<i>respectively</i>)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Phathom Pharmaceuticals, Inc.
US agent, if applicable	N/A

*Proposed trade name

Submission(s) Assessed	Document Date	Discipline(s) Affected
0002	September 3, 2021	All
0012	December 17, 2021	All
0018	January 18, 2022	Drug Substance, Drug Product, Process
0020	January 24, 2022	Process
0021	January 25, 2022	Biopharmaceutics
0024	January 31, 2022	Environmental Analysis
0030	February 17, 2022	Drug Product
0039	April 8, 2022	Drug Product
0041	April 21, 2022	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Karina Zuck	Katherine Windsor
Drug Product	Molly Lee	Dorota Matecka
Manufacturing	Jiao Yang	Steve Rhieu
Microbiology	Jiao Yang	Steve Rhieu
Biopharmaceutics	Min Kang	Elsbeth Chikhale
Environmental Analysis	James Laurenson (<i>refer to Drug Product Review</i>)	
Laboratory (OTR)	N/A	
RBPM	Anh-Thy Ly	
ATL	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs*:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	September 2, 2021	Review by Dr. Udofot
	III				N/A*	
	III				N/A*	

*Sufficient information provided in the NDA – refer to the Drug Product Chapter

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
IND	144399	Development of dual therapy pack
ANDA	64076	Amoxicillin capsules used in the co-package (LoA provided in the NDA)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	Adequate (acceptance criteria for impurities)	Refer to Drug Substance and Drug Product reviews	Dr. Leah Rosenfeld
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product (co-packaged vonoprazan tablets and amoxicillin capsules). In addition, all manufacturing and testing facilities have been found acceptable by the Office of Pharmaceutical Manufacturing Assessment (OPMA). Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

VOQUEZNA DUAL PAK, is a co-packaged product containing vonoprazan, a PCAB, and amoxicillin, a penicillin class antibacterial, indicated for the treatment of *H. pylori* infection in adults. Specifically, the proposed commercial drug product (dual therapy pack) contains: vonoprazan tablets, 20 mg, and, previously approved, amoxicillin capsules, 500 mg, co-packaged in one blister card, on which each tablet or capsule is contained within its own blister cavity.

The proposed drug product combination received Fast Track (FT) and Qualified Infectious Disease Product (QIDP) designations on January 22, 2021, and May 16, 2021, respectively (for the treatment of *Helicobacter pylori* infection).

Proposed Indication(s) including Intended Patient Population	Treatment of <i>Helicobacter pylori</i> infection in adults.
Duration of Treatment	The recommended dosage regimen is vonoprazan 20 mg twice daily (morning and evening) plus amoxicillin 1,000 mg, three times a day (morning, mid-day, and evening), with or without food, for 14 days.
Maximum Daily Dose	40 mg vonoprazan/3000 mg amoxicillin
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

This OPQ Assessment Addendum includes the Labeling Review and the Addendum to Drug Product Review, which addresses several issues related to drug product, pending at the time of the OPQ Assessment # 1. For other discipline reviews, including Drug Substance(s), Biopharmaceutics, and Manufacturing, refer to the OPQ Assessment # 1 (dated February 7, 2022, in DARRTS).

Drug Product: Adequate

The proposed drug product is a co-package or oral use containing vonoprazan tablets and amoxicillin capsules. The CMC information for vonoprazan tablets, 20 mg, is referenced to NDA 215152. Amoxicillin capsules, 500 mg, used in the co-package are commercially available, approved under ANDA 64076, and manufactured by Sandoz GmbH (Austria). For detailed review of these individual two drug product components of the proposed co-package (dual therapy pack), refer to the Drug Product Review included in the OPQ Review of NDA 215152.

Most of the drug product quality aspects were reviewed and found acceptable in the Drug Product Review included in the OPQ Assessment # 1. However, several issues were listed as pending and they included: 1) (b) (4) (statement of compliance); 2) drug product shelf-life; and 3) environmental assessment.

(b) (4)

Drug product shelf-life

As agreed in a pre-NDA CMC meeting, the stability data generated for the triple therapy blister pack have been used to support the application for the dual (b) (4) pack as identical packaging materials are used in the dual and triple therapy packs/blisters. Although the stability data package submitted in the initial NDA (NDA 215152) included limited data for the proposed commercial package presentation, a significant amount of supportive stability data was submitted for individual components, and a (b) (4)-month shelf life was proposed by the Applicant for the triple and dual packs. During the NDA review, additional stability information was provided via several amendments. Based on the analysis of the overall stability data provided (which included some unexplained fluctuating trends and inconsistencies for one of the vonoprazan impurities, related substance (b) (4) a shelf-life of 24 months has been granted for the triple and dual packs to be stored at room temperature. Additionally, a release

acceptance criterion was added for vonoprazan related substance (b) (4) in the drug product specification to help to ensure (b) (4) does not go out of specification before the 24-month expiry date (*for detailed discussion of stability data and the calculation of the expiration dating for triple and dual packs, refer to the Drug Product Review Addendum, below, and for NDA 215152*).

Environmental Assessment (EA)

Additional information regarding Environmental Assessment was requested by James Laurenson (EA Team) and submitted in the amendment dated January 31, 2022. Based on the overall information provided, the claim of categorical exclusion has been found acceptable.

For further details refer to the Drug Product Review, below.

Labeling: Adequate

The proposed prescribing information (PI), container label, and carton labeling were found to generally include the necessary information from the product quality perspective. Several revisions and additions have been recommended in the applicable to the product quality sections of the PI (Sections 3, 11 and 16); also, for the container/blister label and carton labeling. Labeling recommendations have been communicated and accepted by the Applicant. *For details, refer to the Labeling Review, below.*

Manufacturing: Adequate

Manufacturing process and facilities for vonoprazan tablets, and facilities for amoxicillin capsules are same as in the sister application, NDA 215152, currently also under review. Both, the manufacturing process for vonoprazan tablets and all manufacturing facilities were found adequate for NDA 215152. All facilities involved in the manufacture of the dual therapy packs are the same as for the triple therapy packs, and the overall "Approve" recommendation for manufacturing facilities for NDA 215153 was entered into Panorama on February 3, 2022. *For further details refer to the Manufacturing Integrated Assessment included in the OPQ Assessment # 1 for this NDA and NDA 215152, in DARRTS.*

In addition, in the email to RBPM (dated April 28, 2022), Dr. Jiao Yang has confirmed that all facilities remain in adequate status.

C. List of Pending Issues: None



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Lee

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Dorota
Matecka

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CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: It is proposed to use one label for NDAs 215152 and 215153. See labeling review for NDA 215152 for review of PI.

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels



3-D images of the blister card were also submitted to the NDA in Seq. # 0040:

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name (font size and prominence)	Adequate	Full Product Title, including dosage form for each component, must appear on label. Comment to applicant: Update the label to include the full product title, including dosage form and strength. For example, product title should be revised to read: "(b) (4) Triple Pak (Vonoprazan tablets; amoxicillin capsules; clarithromycin tablets)" Phathom submitted carton/container revisions with the Product Title: VOQUEZNA DualPak vonoprazan tablets 20 mg amoxicillin capsules 500 mg The following recommendation was sent: For the container labels and carton labeling of both the Triple Pak and Dual Pak, revise the established names to include a comma separating the established name from the strength. For example: VOQUEZNA DualPak vonoprazan tablets, 20 mg amoxicillin capsules, 500 mg

Strength(s) in metric system	Adequate	Comment to applicant from DMEPA with proposed OPQ edit: 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, 500 mg per capsule**"
Route(s) of administration	Adequate	Added co-packaged for oral use to product title on carton
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Equivalency statements are present: *Each tablet contains 20 mg of vonoprazan (equivalent to 26.72 mg of vonoprazan fumarate). **Each capsule contains amoxicillin trihydrate (equivalent to 500 mg of amoxicillin).
Net contents (e.g., tablet count, volume of liquid)	Adequate	Net number of capsules/tablets not present on carton label, It does state: "14 Daily Treatment Packs" and "Each Daily Treatment Pack Contains OPQ recommended to applicant: Update the label to include information on the net contents. For example, container label should include: "Carton contains 28 tablets and 84 capsules"
"Rx only" displayed on the principal display	Adequate	

NDC	Adequate	NDC number on blister pack matches with that proposed in (and removed from) the PI. Validation and verification of NDC #s is covered by the Office of Unapproved Drugs and Labeling Compliance. Comment to applicant from DMEPA: 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."
Lot number and expiration date	Adequate	Lot and expiration date were missing. Comment to applicant from DMEPA: 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 YYYYMM-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 humanreadable 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.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Revised to include: Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Linear bar code was absent. Comment to applicant from DMEPA: 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).

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor/packer	Adequate	Manufacturing information is listed on each cut for each tablet/capsule Manufacturing information is listed for each component on the carton label.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap over seal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	We recommended the removal of "(b) (4)" from the clarithromycin tablets and amoxicillin capsules product names throughout the label to reduce clutter and increase readability and clarity.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

Overall Assessment and Recommendation:

All OPQ recommendations were implemented in the prescribing information and carton/container labels.

Primary Drug Product Assessor Name and Date:

Molly Lee, Ph.D., Branch 2, ONDP Division of New Drug Products I, 4/27/2022

Secondary Assessor Name and Date:

*Dorota Matecka, Ph.D., Branch 2, ONDP Division of New Drug Products I,
4/27/2022*



Molly
Lee

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Dorota
Matecka

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/s/

DOROTA M MATECKA
05/02/2022 09:47:33 AM

RECOMMENDATION *Pending*

☐ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215153 Assessment # 1

Drug Product Name	(b) (4) Dual Pak* (vonoprazan tablets; amoxicillin capsules)
Dosage Form	Tablets and capsules
Strength	20 mg; 500 mg (<i>respectively</i>)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Phathom Pharmaceuticals, Inc.
US agent, if applicable	N/A

*Proposed trade name

Submission(s) Assessed	Document Date	Discipline(s) Affected
0002	September 3, 2021	All
0012	December 17, 2021	All
0018	January 18, 2022	Drug Substance, Drug Product, Process
0020	January 24, 2022	Process
0021	January 25, 2022	Biopharmaceutics
0024	January 31, 2022	Environmental Analysis

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Karina Zuck	Katherine Windsor
Drug Product	Molly Lee	Dorota Matecka
Manufacturing	Jiao Yang	Steve Rhieu
Microbiology	Jiao Yang	Steve Rhieu
Biopharmaceutics	Min Kang	Elsbeth Chikhale
Environmental Analysis	James Laurenson (<i>refer to Drug Product Review</i>)	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs*:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	September 2, 2021	Review by Dr. Udofot
	III				N/A*	
	III				N/A*	

*Sufficient information provided in the NDA – refer to the Drug Product Chapter

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
IND	144399	Development of dual therapy pack
ANDA	64076	Amoxicillin capsules used in the co-package (LoA provided in the NDA)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	Adequate (acceptance criteria for impurities)	Refer to Drug Substance and Drug Product reviews	Dr. Leah Rosenfeld
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The majority of the CMC information provided in the NDA for the drug substances and the proposed drug product was found to be adequate. However, there are several outstanding issues that will need to be resolved, such as a (b) (4) compliance statement for the proposed commercial container-closure system and acceptability of the proposed expiration dating for the drug product. Also, the proposed labeling, including the package insert and the container and carton labels, are presently under review. The manufacturing and testing facilities have been found acceptable and the Overall Manufacturing Inspection Recommendation (OMIR) of "Approve" was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on February 3, 2022. However, due to the pending resolution of the remaining issues for the drug product, the final OPQ approvability recommendation for this NDA is currently **pending**.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

(b) (4) DUAL PAK, which has been developed for the treatment of *Helicobacter pylori* infection in adults, is a co-packaged combination product containing vonoprazan, a new potassium-competitive acid blocker (PCAB) and amoxicillin, a penicillin class antibacterial.

The proposed commercial drug product (dual therapy pack) contains vonoprazan tablets, 20 mg, and previously approved amoxicillin capsules, 500 mg, co-packaged in one blister card, on which each tablet or capsule is contained within its own blister cavity.

The proposed drug product combination received Fast Track (FT) and Qualified Infectious Disease Product (QIDP) designations on January 22, 2021 and May 16, 2021, respectively (for the treatment of *Helicobacter pylori* infection).

Proposed Indication(s) including Intended Patient Population	Treatment of <i>Helicobacter pylori</i> infection in adults.
Duration of Treatment	The recommended dose is vonoprazan 20 mg given twice daily in the morning and evening plus amoxicillin 1000 mg, taken three times a day in

	the morning, mid-day, and evening, for 14 days (to be taken with or without food).
Maximum Daily Dose	40 mg vonoprazan/3000 mg amoxicillin
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

This NDA provides for a combination of two drugs (vonoprazan and amoxicillin) to be used for the treatment of Helicobacter pylori infection. The Applicant has concurrently submitted a second NDA (NDA 215152) for a combination of vonoprazan, amoxicillin and clarithromycin (triple therapy pack) for the same indication. These drug products have been developed in DAI via INDs 144399 and 143190, respectively. Amoxicillin is a known and approved antibacterial drug, while vonoprazan is an NME (b) (4)

The drug product submitted in the current NDA (dual therapy pack) is a combination of vonoprazan tablets, 20 mg, and previously approved, amoxicillin capsules, 500 mg, co-packaged in a blister card, on which each tablet or capsule is contained within its own blister cavity. The proposed commercial dual therapy blister card contains two (2) vonoprazan tablets, 20 mg, and six (6) amoxicillin capsules, 500 mg. Each blister card contains the dosing regimen for one day. The proposed commercial packaging presentation includes 14 triple therapy blister cards packaged in a carton as a (b) (4) *pack to cover the entire course of treatment (14 days).*

The CMC information for amoxicillin capsules and clarithromycin tablets used in dual and triple therapy packs, has been provided via a reference to approved ANDAs 64076 and 665136, respectively. The CMC information for vonoprazan and vonoprazan tablets has been provided in NDA 215152.

Drug Substance: Adequate

Most of the CMC information regarding vonoprazan fumarate drug substance is referenced to NDA 215152. The information for amoxicillin drug substance is referenced to DMF (b) (4) (b) (4). (b) (4) The applicant provided LoAs to the referenced DMF and approved ANDA 64076. DMF (b) (4) has been found adequate per the latest review dated September 2, 2021.

Following previous agreements with the Agency, the current NDA includes general information, manufacturers, a specification, and batch data for both drug substances, vonoprazan fumarate and amoxicillin, to be used in the proposed drug product, dual therapy pack. Overall information provided for these two drug substances in support of the proposed drug product, was found adequate by the Drug Substance Reviewer.

For further details refer to the Drug Substance Review, below.

Drug Product: Adequate

The proposed drug product is a co-package or oral use containing vonoprazan tablets and amoxicillin capsules. The CMC information for vonoprazan tablets, 20 mg, is referenced to NDA 215152. Amoxicillin capsules, 500 mg, used in the co-package, similarly to NDA 215152, are commercially available, approved under ANDA 64076, and manufactured by Sandoz GmbH (Austria). For detailed review of these individual two drug product components of the proposed co-package (dual therapy pack), refer to the Drug Product Review included in the OPQ Review of NDA 215152.

The container closure system (CCS) proposed for the dual therapy pack is a (b) (4) blister with separate cavities for two vonoprazan and six amoxicillin capsules. It is identical to the CCS used for the triple therapy pack. Therefore, in a pre-NDA CMC meeting on January 7, 2021, it was agreed that the triple therapy blister pack stability data could be used to support the NDA for the dual (b) (4) pack. Overall information provided for the container closure system was found acceptable by the Drug Product Reviewer; however, a statement that the container closure system is (b) (4) was not provided. In response to the Agency IR, the Applicant stated that the blister packs will be tested to confirm compliance with applicable regulations prior to commercialization. A follow-up discussion with the Applicant is needed to better understand their plans for testing and providing this required statement to the NDA.

Although the stability data package (mostly submitted in the NDA 215152) includes limited data for the proposed commercial package presentation, a significant amount of supportive stability data was submitted for the individual components, and a (b) (4) month shelf life was proposed by the Applicant for both, triple and dual therapy packs. There were no out of specification results reported in any of the studies; however, some unexplained fluctuating trends and inconsistencies were observed across the data, for example, for some of the vonoprazan impurities. Based on these observations, a shelf-life of 24 months was determined to be more reasonable for this product. As described in the review of NDA 215152,

the issue of the expiration dating for both triple and dual packs will be discussed with the Applicant and further addressed in an addendum to this review.

Additional information regarding Environmental Assessment was requested by James Laurenson (EA Team) and submitted on in the amendment dated January 31, 2022. Review of this information is currently pending and will be included in the addendum.

For further details refer to the Drug Product Review, below.

Labeling: Choose an item.

The proposed prescribing information (PI), container labels, and the carton labeling were found to generally include the necessary information. Several revisions and additions have been recommended in the applicable to the product quality sections of the PI (Sections 3, 11 and 16); also, for the container/blister label and carton labeling. Labeling recommendations have been communicated to OND PM and are under discussion with DMEPA. The labeling review will be included in the addendum to the this review.

Manufacturing: Adequate

Manufacturing process and facilities for vonoprazan tablets, and facilities for amoxicillin capsules are same as in the sister application, NDA 215152, currently also under review. Both, the manufacturing process for vonoprazan tablets and all manufacturing facilities were found adequate for NDA 215152. Since all facilities involved in the manufacture of the dual therapy packs are the same as for the triple therapy packs, the overall "Approve" recommendation for manufacturing facilities for NDA 215153 was entered into Panorama on February 3, 2022.

For further details refer to the Manufacturing Integrated Assessment, below, and OPQ Review of NDA 215152, in DARRTS.

Biopharmaceutics: Adequate

The Biopharmaceutics review focused on the evaluation of (1) the in vitro dissolution data and the acceptance criterion for the proposed drug product, and (2) the bridging between [i] different formulations of vonoprazan tablets, [ii] over-encapsulated vonoprazan tablets and un-encapsulated vonoprazan tablets, and [iii] vonoprazan tablets manufactured at two different sites having two different images (e.g., (b) (4) tablets with strength printed vs. (b) (4) tablets with strength debossed).

Dissolution:

The following in vitro dissolution methods and dissolution acceptance criteria shown in the table below are found acceptable for batch release and stability testing:

Drug Product	Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
Vonoprazan ¹ Tablets	USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.05 M Acetate Buffer (pH 4.5)	Q = (b)(4)% at 15 minutes
Amoxicillin ² Capsules	USP I (Basket)	100 rpm	900 mL/ 37 °C	Water	Q = (b)(4)% in 90 minutes

¹ The QC dissolution method for Vonoprazan Tablets had been approved during the IND stage. The approved Dissolution Method Development Report can be found at the following link (applicable for (b)(4) IND 144399, IND 143190): <https://darts.fda.gov/darts/ViewDocument?documentId=090140a8061ee7>

² The QC dissolution method for Amoxicillin Capsules had been evaluated and approved as part of the ANDA 064076 (Sandoz)

Bridging:

Vonoprazan Tablets:

During development of vonoprazan tablets, 20 mg, formulations T2, T3, and T4 were used. The bridge between formulations/batches studied in the clinical trials and the proposed commercial drug product have been evaluated and determined to be adequately bridged via in vitro dissolution data for the following: (1) formulations T2, T3, and T4, (2) over-encapsulated tablet to un-encapsulated tablet, (3) drug product manufacturing sites, and (4) tablet Image.

Amoxicillin Capsules:

The same commercially available generic amoxicillin capsules (ANDA 64076, Sandoz GmbH) that were used in the Pivotal Study (HP-301) are being proposed for the commercial drug product (dual therapy packs). Therefore, bridging is not needed.

The overall Biopharmaceutics information submitted in the NDA was found adequate by the Reviewer. For further details refer to the Biopharmaceutics Review, below.

Microbiology: Adequate

The proposed drug product is a co-package of two drug products, oral solid dosage forms. Therefore, a separate microbiology review was not needed. The microbiological controls proposed for the finished commercial drug product were addressed by the Process Reviewer (refer to the Manufacturing Integrated Assessment, below, and OPQ Review of NDA 215152, in DARRTS).

C. List of Pending Issues

Drug Product:

The following issues are currently pending/are under discussion and will be addressed in the addendum to this review:

- i. (b) (4) *proposed commercial container closure system*
- ii. *Drug product expiration dating*
- iii. *Environmental assessment*
- iv. *Labeling*

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NDA/ Type of Submission: NDA 215153-ORIG-1; 505(b)(2)
Applicant Name: Phathom Pharmaceuticals Inc
Drug Product Name & Strength: (b) (4) Dual Pak (Vonoprazan Tablets 20 mg and Amoxicillin Capsules (b) (4) 500 mg)
Route of Administration: Oral
Submission Date: 09/03/2021 (Original Submission)
Primary Biopharmaceutics Reviewer: Min (Sammie) Kang, Pharm.D., M.S.
Secondary Biopharmaceutics Reviewer: Elsbeth Chikhale, Ph.D.

BACKGROUND AND SUMMARY

The Applicant submitted this 505(b)(2) NDA seeking approval for (b) (4) Dual Pak (Vonoprazan Tablets 20 mg and Amoxicillin Capsules (b) (4) 500 mg). Vonoprazan belongs to a new class of acid-inhibitory agents called potassium-competitive acid blocker (PCAB). The current NDA submission has been granted Qualified Infectious Disease Product (QIDP) designation (5-5-2021) and Fast Track designation on (1-22-2021). The proposed drug product (co-packaged dual pack) is indicated for the treatment of *Helicobacter pylori* (H pylori) infection. The proposed dose is Vonoprazan 20 mg BID (twice daily) and Amoxicillin 1000 mg TID (three times a day) for 14 days. This application is primarily supported by clinical safety and efficacy data obtained from two Pivotal Clinical Phase 3 Studies (HP-301 and TAK-438/CCT-401), and relies in part on FDA's previous findings of safety and efficacy for the co-packaged approved generic drug product, Amoxicillin Capsules.

This Biopharmaceutics Review focuses on the evaluation of (1) the in vitro dissolution data and the acceptance criterion as a quality control (QC) for the proposed drug product, and (2) the bridging between [i] different formulations of vonoprazan tablets, [ii] over-encapsulated vonoprazan tablets and un-encapsulated vonoprazan tablets and [iii] vonoprazan tablets manufactured at two different sites having two different images (e.g., (b) (4) tablets with strength printed vs. (b) (4) tablets with strength debossed).

In Vitro Dissolution Methods and Acceptance Criteria: ACCEPTABLE

The following in vitro dissolution methods and dissolution acceptance criteria shown in the table below are found acceptable for the Quality Control (QC) testing of (b) (4) Dual Pak (Vonoprazan Tablets 20 mg and Amoxicillin Capsules (b) (4) 500 mg), for batch release and stability testing:

Drug Product	Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
Vonoprazan ¹ Tablets	USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.05 M Acetate Buffer (pH 4.5)	Q = (b) (4) % at 15 minutes
Amoxicillin ² Capsules	USP I (Basket)	100 rpm	900 mL/ 37 °C	Water	Q = (b) (4) % in 90 minutes

¹ The QC dissolution method for Vonoprazan Tablets had been approved during the IND stage. The approved Dissolution Method Development Report can be found at the following link (applicable for (b) (4) IND 144399, IND 143190):
<https://darts.fda.gov/darts/ViewDocument?documentId=090140af8061ece7>

² The QC dissolution method for Amoxicillin Capsules had been evaluated and approved as part of the ANDA 064076 (Sandoz)

Biowaiver Request: NOT APPLICABLE

The Applicant submitted a BCS-based biowaiver request³ to support the formulation changes to the vonoprazan tablet during clinical development (T1 to T4). However, the formulation changes (b) (4)] between the T1 and T2, T2 and T3, and T3 and T4 formulations are deemed minor (e.g., within $\pm 10\%$) and can be bridged by dissolution profile comparison if needed. Therefore, a bioequivalence study will not be necessary (i.e., the BCS-based biowaiver is not required to bridge formulations T1 to T4).

Bridging: ACCEPTABLE

Vonoprazan Tablets: During the drug development of Vonoprazan Tablets, 20 mg, formulations T2, T3, and T4 were used. The bridge between formulations/batches studied in the clinical trials and the proposed commercial drug product have been evaluated and was determined to be adequately bridged via in vitro dissolution data for the following: (1) Formulations T2, T3, and T4, (2) Over-encapsulated Tablet to Un-encapsulated Tablet, (3) Drug Product Manufacturing sites, and (4) Tablet Image. Please reference Section 7 of the review for the details.

Amoxicillin Capsules: The same commercially available generic amoxicillin capsules (ANDA 064076, Sandoz GmbH) that were used in the Pivotal Study (HP-301) are being proposed for the commercial (b) (4) Dual Therapy (b) (4) packs. Therefore, bridging is not needed.

Overall Recommendation: From the Biopharmaceutics perspective, NDA 215152 for the proposed (b) (4) Dual Pak (Vonoprazan Tablets 20 mg and Amoxicillin Capsules (b) (4) 500 mg), is **Adequate** and recommended for Approval.

³ [NDA215152 \(215152 - 0015 - \(15\) - 2022-01-03 - ORIG-1 /Clinical/Response To Information Request\) - Request for Waiver for in vivo Studies](#)

BIOPHARMACEUTICS ASSESSMENT**1. List of Submissions Reviewed:**

SDN	Received date	Document
2	09/03/2021	Original NDA submission
12	12/17/2021	Quality/Response to Quality/Biopharmaceutics IR #1
18	01/18/2022	Quality/Response to Biopharmaceutics IR #1

2. BCS Designation:

Solubility of Vonoprazan: The vonoprazan fumarate drug substance is considered highly soluble per the BCS classification as evidenced by its high solubility (> 0.08 mg/mL [20 mg/250 mL]) across the physiologic pH (pH 1-7), as described below in Table 1.

Table 1: Solubility vs. pH at 37 °C

Test buffer	Solubility as TAK-438F in Test Buffer	
	Average [mg/mL]	RSD [%]
pH 1.2	19.9	0.3
pH 3.6	4.83	0.6
pH 4.5	5.02	0.6
pH 5.6	4.64	1.9
pH 6.8	4.62	2.6

Permeability of Vonoprazan: The Applicant has submitted the permeability data⁴ of vonoprazan based on in vitro intestinal permeability study using Caco-2 cell monolayers. (b) (4)

Dissolution of Vonoprazan: The in vitro dissolution profile of Vonoprazan Tablets (20 mg) in multi-pH (b) (4) show a very rapid dissolution ($\geq$ (b) (4) % dissolution within 15 minutes).

Reviewer's comments: Based on the above information, Vonoprazan may be classified as highly soluble. (b) (4)
(b) (4). The BCS (b) (4) designation is not needed for the approval of this NDA, since a BCS-based biowaiver is not needed for the approval of this NDA.

For the solubility of Amoxicillin drug substance, ANDA 064076 should be referenced.

4 (b) (4)

5 (b) (4)

3. Formulation Composition:

Table 2 shows the formulation composition of the Vonoprazan Tablets, 20 mg (T2, T3, and T4) used during the drug product development.

Table 2: Composition of Formulation T2**Table 3: Composition of Formulation T3**

(b) (4)

Table 4: Composition of Formulation T4 (final proposed formulation)

Component	Function	(b) (4) 20 mg tablet (mg)
Vonoprazan fumarate		26.72
(Vonoprazan)	Active	(20)
(b) (4) (4)mannitol		(b) (4)
Microcrystalline cellulose ^a		
Hydroxypropyl cellulose		
Fumaric acid		
Croscarmellose sodium		
Magnesium stearate		
Hypromellose ^b		
(b) (4)		
Titanium dioxide		
Red ferric oxide		
(b) (4)		
Total		
Parentheses indicate content in terms of the free base of vonoprazan (salt conversion factor: 1.556). Unit: mg/tablet		
(b) (4)		

(b) (4)

. The drug product manufacturing process for the final proposed immediate-release oral Vonoprazan Tablets, 20 mg, include: (b) (4)

For the formulation composition information and manufacturing process of Amoxicillin Capsules refer to ANDA 064076.

4. Dissolution Method Development:

Vonoprazan Tablets: The proposed QC dissolution method for the proposed Vonoprazan Tablets, 20 mg, had been found acceptable as part of the IND submissions ((b) (4) IND 144399 [SDN-23], IND 143190 [SDN-31]). The review of the complete Dissolution Method Development Report can be found at the following link (finalized on 10-19-2021):

<https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af8061ece7>

Amoxicillin Capsules: The proposed QC dissolution method for Amoxicillin Capsules 500 mg has been evaluated and approved as part of the ANDA 064076 (Sandoz)

The following proposed QC dissolution methods are found acceptable:

Drug Product	Apparatus	Speed	Volume/ Temp	Medium
Vonoprazan Tablets	USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.05 M Acetate Buffer (pH 4.5)
Amoxicillin Capsules	USP I (Basket)	100 rpm	900 mL/ 37 °C	Water

5. Dissolution Data and Acceptance Criterion:

The Applicant's registration stability lots for the Proposed Triple (b) (4) Pack Blister Card (as supportive of the Dual Therapy blister cards) are described below in Table 3.

**Table 3: The Registration Lots for the Proposed Triple (b) (4) Pack Blister Card
(as supportive of the Dual Therapy blister cards)**

Manufacturer	(b) (4)		Amoxicillin Capsules 500 mg	Clarithromycin Tablets 500 mg
			Sandoz GmbH (Kundl, Austria)	Sandoz S.R.L. (Targu Mures, Romania)
Lot 1	32066685	11920534	KZ8535	KZ2349
Lot 2	32066688	11921111	KZ8536	KZ2349
Lot 3	32066690	11921112	KZ8538	KZ2349

1—Vonoprazan Tablets: The in vitro dissolution profiles of the clinical lots for the Vonoprazan Tablets, 20 mg (Study HP-301, formulation T4, Bulk Lot# H1223 [PCI Kit ID#: 504716, 500317, 504592]⁶) shows a very rapid dissolution ($\geq$ (b) (4) % dissolution within 15 minutes) using the proposed QC dissolution method as shown in Table 4 below.

⁶ [NDA215152 \(215152 - 0018 - \(18\) - 2022-01-18 - ORIG-1 /Quality/Response To Information Request\) - Pharm Dev - Formulation Development - Original - \(b\) \(4\)-0001667 \(#39\)](#)

Table 4: Dissolution Profile of the Clinical Lot of Vonoprazan Tablets, 20 mg (H1223)

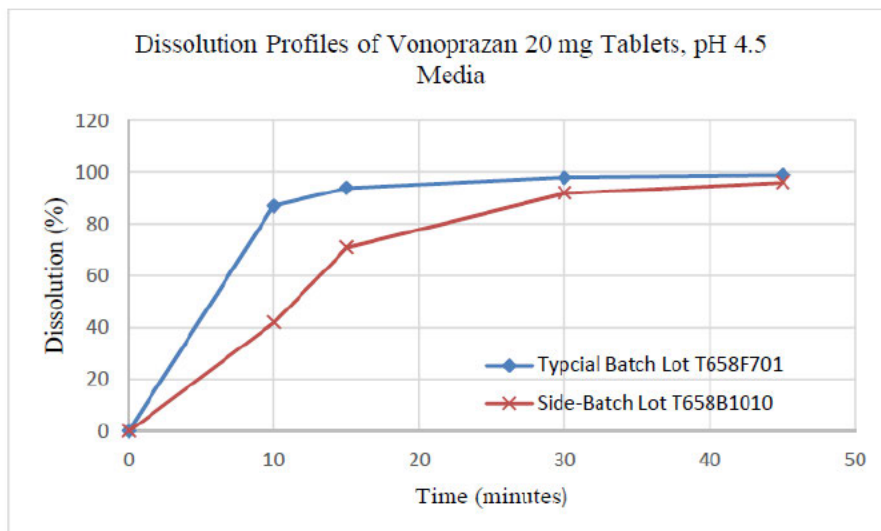
Media	Sample	10 min	15 min	30 min	45 min
pH 4.5 (20 mg)	Blinded 504716	(b) (4)			
	Blinded 500317				
	Blinded 504592				

The formulation used in clinical study TAK-438/CCT-401 was formulation T3 and it also shows a very rapid dissolution ($\geq$ (b) (4) % dissolution within 15 minutes) in multi-pH media (USP Apparatus II, in 900 mL at 50 rpm; pH (b) (4)); please reference Figure 2 under Section 7. Also, the proposed registration batches ((b) (4) lot # 11888539 and (b) (4) Lot#: 4435098) show a very rapid dissolution ($\geq$ (b) (4) % dissolution within 15 minutes) using the proposed QC dissolution method; please reference Table 7 and Figure 4 under Section 7. The Applicant has initially proposed a dissolution acceptance criterion of (b) (4) however, based on the submitted in vitro dissolution profile in the current submission (Table 4 and 7) along with the in vitro dissolution data submitted to support the discriminating ability (Table 5 and Figure 1 below; submitted as part of the Dissolution Method Development Report dated 6-10-20 in the (b) (4) IND-143190, IND-144399) which showed that the dissolution method is capable of discriminating against the aberrant/ side batch (T658B101) if a dissolution criterion of $Q =$ (b) (4) % at 15 minutes is set, the Applicant was requested to tighten the dissolution acceptance criterion to “ $Q =$ (b) (4) % in 15 minutes” via the Information Request dated 12-03-2021. In the Response dated 12-17-2021, the Applicant has agreed to FDA’s recommendation ($Q =$ (b) (4) % at 15 minutes) and has updated relevant sections, M.3.2.P.5.1. and M.3.2.P.8.2., accordingly.

Table 5: Summary of Side batch information vs Typical/ Target batch

Tablet Strength	Lot No.	(b) (4)	Notes
20 mg	T658F701		Typical batch
	T658B101		Side batch

Figure 1: Dissolution Profiles of Typical Batch (Lot T658F701) and Side Batch (Lot T658B101) for Vonoprazan (b) (4) Tablets (20 mg), using the proposed method (Paddle Apparatus, 50 rpm, 0.05 mol/L Acetate Buffer Solution (pH 4.5) (n=6 tablets each))



2—Amoxicillin Capsules: The in vitro dissolution data of the registration lots for the Amoxicillin Capsules, 500 mg (proposed to be co-packaged in the Dual (b) (4) Pack Blister Card) adequately meets the dissolution acceptance criterion that has been evaluated and approved as part of the ANDA 064076 (Sandoz), “Q= (b) (4) at 90 minutes”.

Reviewer’s Comments: The in vitro dissolution data of the clinical and registration batches of Vonoprazan Tablets and Amoxicillin Capsules support the revised (vonoprazan) and proposed (amoxicillin) dissolution acceptance criteria.

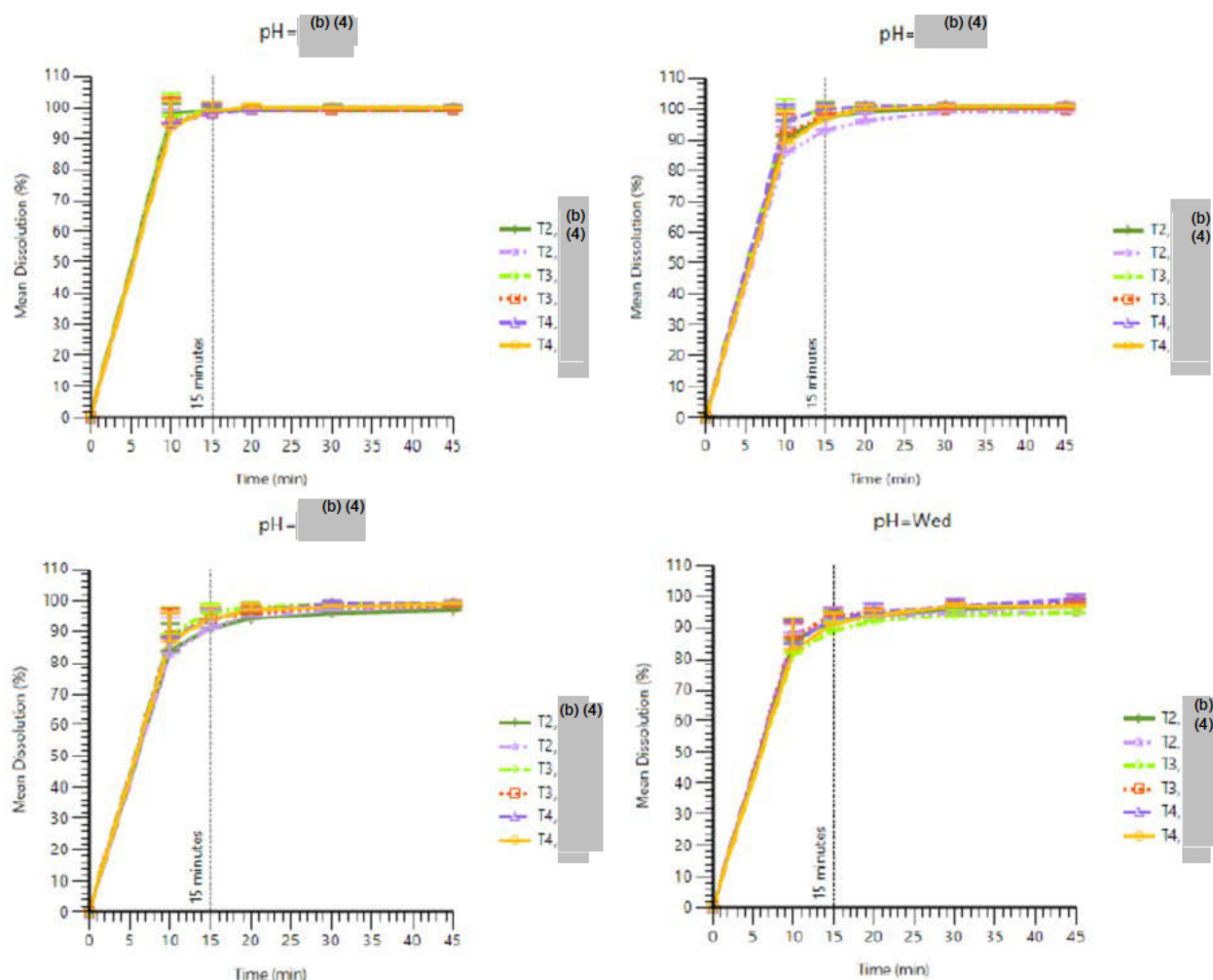
6. Dissolution Stability Data:

No significant trend in the dissolution on stability was observed with the Vonoprazan Tablets and Amoxicillin Capsules packaged in the “(b) (4) Pack Blister Card” and stored for 6-month at accelerated condition ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\%\text{RH} \pm 5\%\text{RH}$), 12-month at intermediate condition ($4=30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\%\text{RH} \pm 5\%\text{RH}$), and 24-months at long-term stability study condition ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\%\text{RH} \pm 5\%\text{RH}$). All stability dissolution results met the proposed dissolution specifications.

7. Bridging:

1—Vonoprazan Tablets: During the drug development of Vonoprazan Tablets, 20 mg, formulations T1⁷, T2, T3, and T4 were used (See Table 2-4, Figure 2). The bridge between formulations/batches studied in the clinical trials and the proposed commercial drug product have been evaluated for the following: (1) Formulations T2, T3, and T4, (2) Over-encapsulated Tablet to Un-encapsulated Tablet, (3) Different drug product manufacturing sites, (4) different tablet image; see Figure 2 and Table 6, below.

Figure 2: Comparative dissolution of Formulations T2, T3, and T4, in Multi-pH (using USP Apparatus II, 900 mL at 50 rpm)



Abbreviations: Wed = Water (Japanese Pharmacopoeia 16th Edition Purified Water)

Table 6: Bridging of Vonoprazan Tablets, 20 mg

Vonoprazan Tablets, 20 mg		
Drug products used in the Pivotal Study (HP-301) Drug Products Manufacturing Site: (b) (4) (8 b)		
Encapsulation	Over-encapsulated (OE) T4 Tablets <u>Bulk Lot#: H1223</u>	Un-encapsulated (UE) T4 Tablets <u>Bulk Lot#: H1223</u> [PCI Kit ID#: 504716, 500317, 504592] ⁹

⁸ Note that (b) (4) for the Clinical Formulations (e.g., T3 and T4 formulations) used in clinical studies other than the Pivotal Study [HP-301]: [NDA215152 \(215152 - 0016 - \(16\) - 2022-01-11 - ORIG-1 /Multiple Categories/Subcategories\) - Batch Analysis - Tablets - \(b\) \(4\) - Original - \(b\) \(4\) 0001609 \(#3\)](#)

⁹ [NDA215152 \(215152 - 0018 - \(18\) - 2022-01-18 - ORIG-1 /Quality/Response To Information Request\) - Pharm Dev - Formulation Development - Original - \(b\) \(4\) -0001667 \(#39\)](#)

	Vonoprazan Tablets, 20 mg Co-packaged in Dual Therapy (b) (4) Pack	
Bulk Tablet Manufacturing Site/ Tablet Image	Clinical drug product manufacturing site:	Proposed commercial drug product manufacturing site:
	(b) (4)	
	<i>with strength information 'printed' on the tablets</i>	<i>with strength information 'debossed V20' on the tablets</i>
	<u>Stability Lots#:</u> <u>11888539, 11888535, 11888583</u> ¹¹ <u>Registration Stability Studies Lot#:</u> <u>11920534, 11921111, 11921112</u>	<u>Registration Stability/ Lot#:</u> <u>4435098</u> ¹²

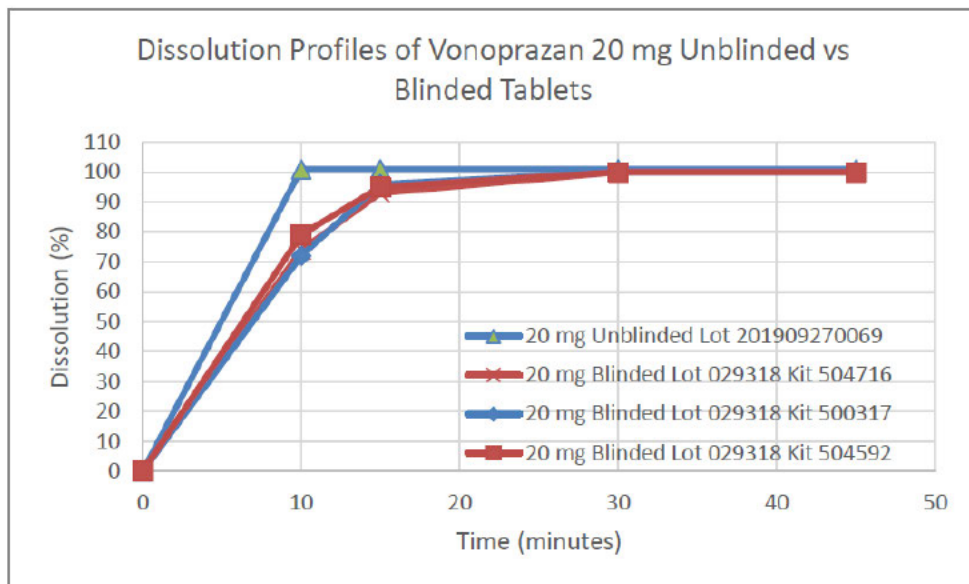
First, there are two versions of vonoprazan drug product used in the Pivotal Study (HP-301): Over-encapsulated (OE) T4 Tablets which has been used to blind patients enrolled in the clinical study, versus the Un-encapsulated (UE) T4 Tablets which has been used as the control (unblind patients) in the clinical study (as described in Table 6 above). In order to appropriately bridge the two drug products, FDA had requested an in vitro dissolution study of the two T4 drug products (OE and UE) at different pH media (e.g., pHs (b) (4) N=12) as part of the communications in the IND (b) (4)/143190/144399—Type A CMC Meeting Request dated 3-19-21. The Applicant provided in vitro dissolution data for Pivotal Study Bulk Lot#: H1223 and compared the OE-T4 Tablets to UE-T4 Tablets using the proposed QC dissolution method i.e., USP Apparatus II [Paddle], 900 mL in pH 4.5 Acetate Buffer at 50 rpm (see General Advice Letter dated 6-2-20 of (b) (4) (b) (4), IND-143190 [SDN-31], IND-144399 [SDN-23]) showing very rapid dissolution for both OE and UE vonoprazan tablets, 20 mg ($\geq$ (b) (4) % in 15 minutes; see Figures 3 below) indicating similarity.

¹⁰ Note that < (b) (4) was also used to manufacture Commercial Scale Stability Lots ((b) (4))

¹¹ [NDA215152 \(215152 - 0016 - \(16\) - 2022-01-11 - ORIG-1 /Multiple Categories/Subcategories\) - Batch Analysis - Tablets - \(b\) \(4\) - Original - \(b\) \(4\)-0001609 \(#17\)](#)

¹² [NDA215152 \(215152 - 0016 - \(16\) - 2022-01-11 - ORIG-1 /Multiple Categories/Subcategories\) - Batch Analysis - Tablets - \(b\) \(4\) - Original - \(b\) \(4\)-0001610 \(#2\)](#)

Figure 3: Comparative Dissolution Profiles for Unblinded (Un-encapsulated) and Blinded (Over-encapsulated) Vonoprazan Tablets, 20 mg (using the proposed QC dissolution method)

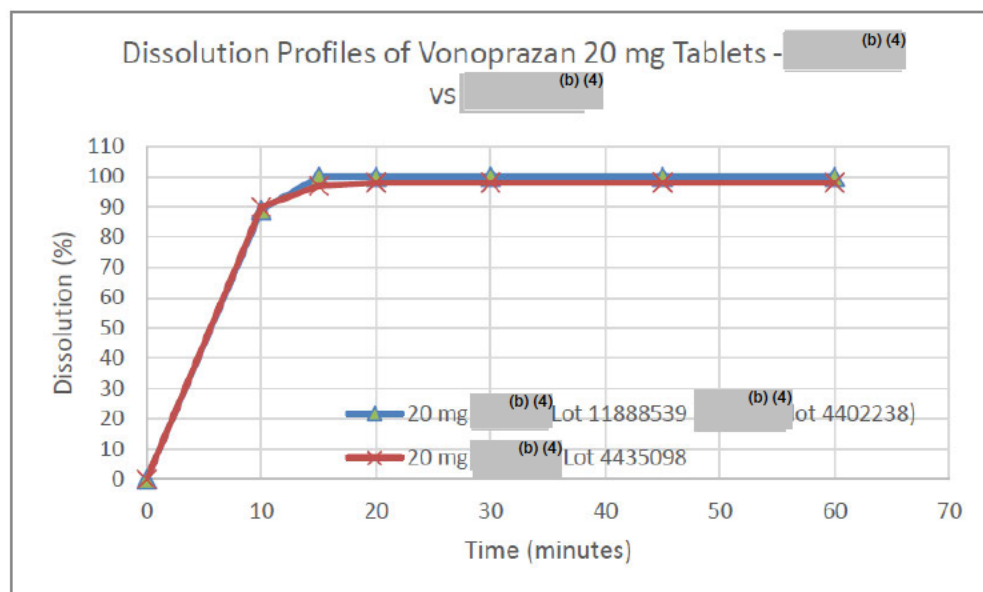


Secondly, the dissolution profiles of tablets manufactured at the (b) (4) site, with printing, were compared to the dissolution profiles of tablets manufactured at the (b) (4) site, which were debossed, using the proposed QC dissolution method which again showed a very rapid dissolution ($\geq$ (b) (4) % in 15 minutes; see Table 17 and Figures 4 below) indicating similarity.

Table 7: Summary of Comparative Dissolution Profile Results for (b) (4) (printed) and (b) (4) (debossed) Tablets, (b) (4) 20 mg, obtained using the proposed dissolution method.

Media	Sample	10 min	15 min	20 min	30 min	45 min	60 min
pH 4.5 (20 mg)	(b) (4)						(b) (4)
	(b) (4)						(b) (4)

Figure 4: Comparative Dissolution Profiles for Vonoprazan Tablets, 20 mg ([strength printed] vs [strength debossed]) obtained using the proposed dissolution method



2—Amoxicillin Capsules: No bridging between Amoxicillin Capsules was necessary because the same generic Amoxicillin Capsules used in the pivotal clinical studies (ANDA 064076, Sandoz GmbH) are being proposed as part of the commercial (b) (4) Dual Therapy (b) (4) packs; see Table 8 below.

Table 8: Comparison of Amoxicillin Capsules used in HP-301 versus Commercial Dual Therapy (b) (4) Pack – bridging evaluation is not applicable

	Drug products used in the Pivotal Study (HP-301)		To-be-marketed Commercial drug products
Amoxicillin Capsules, 500 mg	ANDA 064076, Sandoz GmbH	ANDA 064076, Sandoz GmbH	ANDA 064076, Sandoz GmbH

Reviewer's comments: From the Biopharmaceutics standpoint, as described above, the provided dissolution data for Vonoprazan Tablets, 20 mg, support the bridge between the batches studied in the pivotal clinical trials to the proposed commercial vonoprazan tablets, since all comparative dissolution profiles exhibit > (b) (4) % dissolved in 15 minutes, thus indicating similarity.

No additional bridging is needed for the Amoxicillin Capsules.

8. Compatibility Protocol: ADEQUATE

The Applicant has submitted a Compatibility Protocol (b) (4) FDA requested, via an Information Request dated 01-13-22, that the Applicant modify the comparability protocol, to include the plan to submit a complete dissolution profile for one exhibit drug product batch manufactured using vonoprazan fumarate (b) (4). In the response dated 01-18-22¹³, the Applicant agreed to provide the requested dissolution profile (b) (4) along with the other test results and modified the comparability protocol accordingly. The Applicant's response is acceptable.

9. Biowaiver Request: NOT APPLICABLE

The Applicant submitted a BCS-based biowaiver request¹⁴ to support the formulation changes to the vonoprazan tablet during clinical development (T1 to T4). However, the formulation changes (b) (4) between the T1 and T2, T2 and T3, and T3 and T4 formulations are deemed minor (e.g., within $\pm 10\%$) and can be bridged by dissolution profile comparison if needed. Therefore, a bioequivalence study will not be necessary (i.e., the BCS-based biowaiver is not required to bridge formulations T1 to T4).

¹³ [NDA215152 \(215152 - 0018 - \(18\) - 2022-01-18 - TRIAGE-1 /Electronic Submission/Gateway\) - 2022-01-18 Response to 2022-01-13 FDA CMC Information Request NDA 215152 \(#15\)](#)

¹⁴ [NDA215152 \(215152 - 0015 - \(15\) - 2022-01-03 - ORIG-1 /Clinical/Response To Information Request\) - Request for Waiver for in vivo Studies](#)



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