

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213593Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 213593 Resubmission Assessment 1

Drug Product Name	Konvomep (omeprazole and sodium bicarbonate for oral suspension)
Dosage Form	For oral suspension
Strength	2 mg omeprazole and 84 mg sodium bicarbonate per mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Azurity Pharmaceuticals, Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission, eCTD SN 0039	03/04/2022	DP, OPMA, labeling, and micro
Amendment, SN 0042	03/17/2022	Labeling
Amendment, SN 0043	04/04/2022	DP, OPMA
Amendment, SN 0044	04/29/2022	OPMA
Amendment, SN 0045	05/06/2022	DP, OPMA
Amendment, SN 0046	05/27/2022	OPMA
Amendment, SN 0047	06/01/2022	Labeling
Amendment, SN 0049	07/15/2022	Labeling
Amendment, SN 0050	07/18/2022	Labeling
Amendment, SN 0051	08/17/2022	Labeling
Amendment, SN 0052	08/19/2022	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	N/A*	N/A*
Drug Product	Zhengfang Ge	Hong Cai
Manufacturing	Mesfin Abdi	Yubing Tang
Microbiology	Koushik Paul	Jesse Wells
Biopharmaceutics	N/A*	N/A*
Regulatory Business Process Manager	Melinda Bauerlien	

Application Technical Lead (ATL)	Nina Ni	
Laboratory (OTR)	Josh Shipman, Jamie Mans, and Alicia Hoover	Cynthia Sommers
Environmental	N/A*	N/A*

*: No need for drug substance, biopharmaceutics, and environmental reviewers for this resubmission. The only addition in the drug substance section is submission of updated batch analysis for omeprazole which meet the agreed to specification. The DMF [REDACTED] is up-to-date and remains adequate. There is no new information provided in biopharmaceutics and environmental sections.

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the [Quality Assessment Data Sheet chapter of the NDA IQA Guide](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

Document	Application Number	Description
NDA	213593	Original submission, SN 0001, dated 03/30/2020 Resubmission, SN 0039, dated 03/04/2022

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			



Template Revision: 03

Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



NDA Executive Summary

1. Application/Product Information

NDA Number.	NDA 213593		
Applicant Name	Azurity Pharmaceuticals, Inc.		
Drug Product Name	Konvomep (omeprazole and sodium bicarbonate for oral suspension)		
Dosage Form.	For suspension		
Proposed Strength(s)	2 mg omeprazole and 84 mg sodium bicarbonate per mL		
Route of Administration	Oral		
Maximum Daily Dose	40 mg omeprazole and 1680 mg sodium bicarbonate		
Rx/OTC Dispensed	Rx		
Proposed Indication	For the treatment of active benign gastric ulcer and for reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients		
Drug Product Description	Konvomep (omeprazole and sodium bicarbonate for oral suspension) 2 mg/84 mg per mL is supplied as: A kit containing two bottles: one bottle with child resistant closure of omeprazole USP, a white to off-white powder and one bottle of pre-measured strawberry-flavored slightly hazy red diluent containing sodium bicarbonate at 90 mL, 150 mL, and 300 mL		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store Konvomep kit in the refrigerator, 2°C to 8°C (36°F to 46°F). Store reconstituted suspension of Konvomep in the refrigerator, 2°C to 8°C (36°F to 46°F); discard unused reconstituted suspension after 30 days Keep containers tightly closed. Protect containers from light. Protect containers from freezing.		
Review Team	Discipline	Primary	Secondary



Title:	NDA Executive Summary		
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Template Revision: 03

	<i>Drug Substance</i>	N/A	N/A
	<i>Drug Product/ Labeling</i>	Zhengfang Ge	Hong Cai
	<i>Manufacturing</i>	Mesfin Abdi	Yubing Tang
	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	Koushik Paul	Jesse Wells
	<i>Other (specify): OTR</i>	Josh Shipman, Jamie Mans, and Alicia Hoover	Cynthia Sommers
	<i>RBPM</i>	Melinda Bauerlien	
	<i>ATL</i>	Nina Ni	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

This NDA was issued a complete response due to inadequate control strategy for assuring the identity, strength, purity, quality of the drug product in the previous review cycle. In this resubmission, the applicant has adequately addressed all the deficiencies by: 1) implemented new identification and assay methods for the sodium bicarbonate; 2) adequately addressed discrepancy of the assay and content uniformity methods for the omeprazole; 3) prepared new diluent batches and provided stability data as requested by the Agency; 4) addressed non-approvability issues identified during the last review circle; 5) conducted adequate compatibility studies for the NG/OG tubes to assure the NG/OG tubes are compatible with the



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Template Revision: 03

reconstituted suspension. In addition, the acid-neutralizing capacity (ANC) titration method used for sodium bicarbonate assay in the drug product has been adequately evaluated and found acceptable for quality control and regulatory purposes by OPQ OTR.

OPQ recommends APPROVAL of NDA 213593 for commercialization of Konvomep (omeprazole and sodium bicarbonate for oral suspension). Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate chemistry, manufacturing, and controls (CMC) information to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	N/A
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	N/A
Microbiology	-	Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments: None



Nina
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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The applicant accepted the Agency's recommendation regarding the CMC information in the Prescribing Information. The Prescribing Information is now deemed **ADEQUATE** from CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	KONVOMEF	Adequate

Established name(s)	(omeprazole and sodium bicarbonate for oral suspension)	Adequate It is acceptable to include the dosage form in the established name
Route(s) of administration	oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	For Oral Suspension: 2 mg omeprazole and 84 mg sodium bicarbonate per mL after reconstitution in 90 mL, 150 mL, or 300 mL bottles (3)	Adequate The applicant revised this section per Agency's recommendation during the previous review circle
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	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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Item	Information Provided in the NDA	Assessor's Comments
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)	See proposed Section "2.3 Preparation and Administration" above, copied from the revised PI in the sharePoint	Adequate NG or OG (≥ 8 French) is suggested to be used in the PI. The 8Fr. tubes in the compatibility study shown difficult to push the suspension through but without loss of the suspension. The clinical division has decided acceptable for the 8Fr.

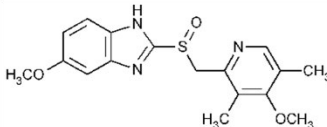
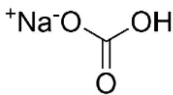
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	For Oral Suspension	Adequate
Strength(s) in metric system	2 mg omeprazole and 84 mg sodium bicarbonate per mL	Adequate The applicant revised this section per Agency's recommendation during the previous review circle
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	2 mg omeprazole and 84 mg sodium bicarbonate per mL of a pink to red hazy, strawberry-flavored liquid after reconstitution in 90 mL, 150 mL, or 300 mL bottles. Each kit contains a bottle of omeprazole as a white to off-white powder and a strawberry-flavored diluent containing sodium bicarbonate as a slightly hazy red liquid [see Description (11) and How Supplied/Storage and Handling (16)]	Adequate The applicant revised this section per Agency's recommendation during the previous review circle
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 labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)



Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	KONVOMEF (omeprazole and sodium bicarbonate for oral suspension)	Adequate
Dosage form(s) and route(s) of administration	for oral suspension	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The strawberry flavored diluent contains sodium bicarbonate and the following inactive ingredients: benzyl alcohol, carboxymethylcellulose sodium, FD&C Red No. 40, poloxamer 188, purified water, simethicone emulsion, sodium citrate (dihydrate), sorbitol solution, strawberry flavor (natural and artificial flavors, propylene glycol, and glycerin), and sucralose	Adequate - The applicant revised this section per Agency's recommendation during the previous review circle
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	
Statement of being sterile (if applicable)	N/A	
Pharmacological/therapeutic class	omeprazole, a PPI, and sodium bicarbonate, an antacid	Adequate

Chemical name, structural formula, molecular weight	Omeprazole: 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, formula is C₁₇H₁₉N₃O₃S, molecular weight is 345.42  Sodium bicarbonate: NaHCO₃, molecular weight is 84.01 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Omeprazole is a substituted benzimidazole, a racemic mixture of two enantiomers that inhibits gastric acid secretion... a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media but has acceptable stability under alkaline conditions. Sodium bicarbonate raises the gastric pH and protects the omeprazole from acid degradation. Sodium bicarbonate is a white crystalline powder. It is soluble in water and insoluble in alcohol. One gram of sodium bicarbonate dissolves in 12 mL of water at 25°C. The pH of a freshly prepared 0.1 molar aqueous solution is 8.3 at 25°C. Aqueous solutions slowly convert to sodium carbonate through loss of carbon dioxide	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
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"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)



Item	Information Provided in the NDA	Assessor's Comments												
HOW SUPPLIED/STORAGE AND HANDLING section														
Available dosage form(s)	for oral suspension	Adequate												
Strength(s) in metric system	2 mg/84 mg per mL	Adequate												
Available units (e.g., bottles of 100 tablets)	90 mL, 150 mL, 300 mL in the Table for strengths and volumes.	Adequate												
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A kit containing two bottles: · one bottle with child resistant closure of omeprazole USP, a white to off-white powder and · one bottle of pre-measured strawberry-flavored slightly hazy red diluent containing sodium bicarbonate <table border="1"> <thead> <tr> <th>NDC Numbers</th><th>Final Volume of KONVOMEF after reconstitution</th><th>Kit Contents</th></tr> </thead> <tbody> <tr> <td>65628-270-03</td><td>90 mL</td><td>Bottle of 0.18 g omeprazole powder and a bottle of diluent containing sodium bicarbonate 7.56 g per 90 mL</td></tr> <tr> <td>65628-270-05</td><td>150 mL</td><td>Bottle of 0.3 g omeprazole powder and a bottle of diluent containing sodium bicarbonate 12.6 g per 150 mL</td></tr> <tr> <td>65628-270-10</td><td>300 mL</td><td>Bottle of 0.6 g omeprazole powder and a bottle of diluent containing sodium bicarbonate 25.2 g per 300 mL</td></tr> </tbody> </table>	NDC Numbers	Final Volume of KONVOMEF after reconstitution	Kit Contents	65628-270-03	90 mL	Bottle of 0.18 g omeprazole powder and a bottle of diluent containing sodium bicarbonate 7.56 g per 90 mL	65628-270-05	150 mL	Bottle of 0.3 g omeprazole powder and a bottle of diluent containing sodium bicarbonate 12.6 g per 150 mL	65628-270-10	300 mL	Bottle of 0.6 g omeprazole powder and a bottle of diluent containing sodium bicarbonate 25.2 g per 300 mL	Adequate
NDC Numbers	Final Volume of KONVOMEF after reconstitution	Kit Contents												
65628-270-03	90 mL	Bottle of 0.18 g omeprazole powder and a bottle of diluent containing sodium bicarbonate 7.56 g per 90 mL												
65628-270-05	150 mL	Bottle of 0.3 g omeprazole powder and a bottle of diluent containing sodium bicarbonate 12.6 g per 150 mL												
65628-270-10	300 mL	Bottle of 0.6 g omeprazole powder and a bottle of diluent containing sodium bicarbonate 25.2 g per 300 mL												
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													

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.)	Prior to dispensing, reconstitute KONVOME [®] P for oral suspension [see <i>Dosage and Administration</i> (2.3)].	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	· Store KONVOME[®]P kit in the refrigerator, 2°C to 8°C (36°F to 46°F). · Store reconstituted suspension of KONVOME[®]P in the refrigerator, 2°C to 8°C (36°F to 46°F); discard unused reconstituted suspension after 30 days. · Keep containers tightly closed. · Protect containers from light. · Protect containers from freezing.	Adequate
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: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	

Include information about child-resistant packaging	child resistant closure for the omeprazole bottle	Adequate
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1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Azurity Pharmaceuticals, Inc. Wilmington, MA 01887 USA	Adequate

2.0 PATIENT LABELING

The following CMC information provided in Medication Guide is adequate



3.0 CARTON AND CONTAINER LABELING

Labels for Omeprazole Bottles (90 mL, 150 mL, 300 mL)

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Carton and Omeprazole Bottles KONVOMEPTM (omeprazole and sodium bicarbonate for oral suspension) Diluent Bottles: DILUENT for Reconstitution of KONVOMEPTM (omeprazole and sodium bicarbonate for oral suspension)	Adequate - The applicant revised this section per Agency's recommendation
Dosage strength	Carton and Omeprazole Bottles 2 mg/84 mg per mL* * When reconstituted, each mL contains 2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP. Diluent Bottles: CONTAINS: sodium bicarbonate, USP, 84 mg/mL.	Adequate - The applicant revised this section per Agency's recommendation
Route of administration	for oral suspension	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	

Net contents (e.g. tablet count)	Carton: 90 mL package: *90 mL final volume EACH KIT INCLUDES: - One bottle containing 0.18 g omeprazole powder - One bottle containing 7.56 g sodium bicarbonate in 90 mL strawberry-flavored Diluent 150 mL package: *150 mL final volume EACH KIT INCLUDES: - One bottle containing 0.3 g omeprazole powder - One bottle containing 12.6 g sodium bicarbonate in 150 mL strawberry-flavored Diluent 300 mL package: *300 mL final volume EACH KIT INCLUDES: - One bottle containing 0.6 g omeprazole powder - One bottle containing 25.2 g sodium bicarbonate in 300 mL strawberry-flavored Diluent Omeprazole Bottles 90 mL package: *90 mL final volume. When reconstituted, each mL contains 2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP. This bottle contains 0.18 g of omeprazole powder. 150 mL package: *150 mL final volume. When reconstituted, each mL contains 2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP. This bottle contains 0.3 g of omeprazole powder. 300 mL package: *350 mL final volume. When reconstituted, each mL contains 2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP. This bottle contains 0.6 g of omeprazole powder. Diluent Bottles 90 mL package: Net Contents: 7.56 g sodium bicarbonate in 90 mL	Adequate - The applicant revised this section per Agency's recommendation
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	150 mL package: Net Contents: 12.6 g sodium bicarbonate in 150 mL 300 mL package: Net Contents: 25.2 g sodium bicarbonate in 300 mL	
“Rx only” displayed on the principal display	Provided	Adequate
NDC number	Included in cartons, omeprazole bottles and diluent bottles	Adequate The applicant revised this section per Agency’s recommendation
Lot number and expiration date	Included in cartons and omeprazole bottles and on the back of diluent bottles	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store refrigerated 2°C to 8°C (36°F to 46°F). Discard 30 days after reconstitution	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Included in cartons, omeprazole bottles and diluent bottles	Adequate The applicant revised this section per Agency’s recommendation

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Provided	Adequate
Medication Guide (if applicable)	Carton: Recommended Dosage: See Full Prescribing Information Each Kit Include: One Full Prescribing Information One Medication Guide	Adequate
No text on Ferrule and Cap overseal	N/A	
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	Carton TO THE PHARMACIST IMPORTANT: Add contents of strawberry-flavored diluent to the bottle containing omeprazole powder according to the preparation steps in the Full Prescribing Information. Shake well before each use Instruct the patient to: • Store refrigerated 2°C to 8°C (36°F to 46°F) • Discard 30 days after reconstitution • Avoid contact with eyes • Keep container tightly closed • Keep out of reach of children • Protect from light • Protect from freezing Omeprazole Bottle: IMPORTANT NOTE TO PHARMACIST: Must Reconstitute before dispensing. This bottle contains 0.18 g of omeprazole powder. Add diluent provided. Diluent Bottle: IMPORTANT NOTE TO PHARMACIST: Add the contents of this bottle to the bottle containing omeprazole powder according to the preparation instructions in the full prescribing information.	Adequate - The applicant revised this section per Agency's recommendation
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Assessment of Carton and Container Labeling: *Adequate*

The applicant revised this section per Agency's recommendation

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

None

Overall Assessment and Recommendation:

The NDA is now ready for approval in its present form per CFR 314.125(b)(6).

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.

*Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT*

Secondary Assessor Name and Date:

Hong Cai, Ph. D.

*Chief, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT*



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MICROBIOLOGY**Product Background:** (b) (4)**NDA:** 213593**Drug Product Name / Strength:** Omeprazole and Sodium Bicarbonate for Oral Suspension; omeprazole USP/sodium bicarbonate USP.**Route of Administration:** Oral Suspension.**Applicant Name:** Azurity Pharmaceuticals, Inc.**Manufacturing Site:**

- Omeprazole USP Powder & Omeprazole for Oral Suspension kit: CutisPharma, Inc. (Azurity Pharmaceuticals, Inc.) 841 Woburn Street, Wilmington MA 01887.
- Strawberry-Flavored Diluent: (b) (4).

Method of Sterilization: This is a nonsterile product.***Review Recommendation:*** Adequate***Theme (ANDA only):*** N/A***Justification (ANDA only):*** N/A***Review Summary:*** (b) (4)**List Submissions Being Reviewed:** 03/04/2022.**Highlight Key Outstanding Issues from Last Cycle:** N/A**Remarks:** The submission is **recommended** for approval on the basis of sterility assurance.**Concise Description Outstanding Issues Remaining:** None.**Supporting Documents:** Microbiology review of N213593MR01.doc, dated 01/13/2021.**List Number of Comparability Protocols (ANDA only):** None.

Product Quality Microbiology Assessment

The NDA-213593 amendment dated 03/04/2022 provides a response to the Agency's deficiency letter (CR) dated 01/28/2021. Please note that the CMC-Microbiology is already found adequate for the NDA-213593 (please see N213593MR01.doc, dated 01/13/2021 for details). All the information that are required to support additional changes are captured below.

INFORMATION TO SUPPORT CHANGES

Reviewer's Assessment: The in this amendment updated the labelling information. For Oral Suspension: 2mg omeprazole and 84mg sodium bicarbonate per mL of a pink to red hazy, strawberry-flavored liquid after reconstitution in 90mL, 150mL, or 300mL diluent bottles. Each kit contains a bottle of omeprazole as a white to off-white powder and a strawberry-flavored diluent containing sodium bicarbonate as a slightly hazy red liquid. No change in dosage form or strength is proposed. No additional changes have been proposed that require Microbiological evaluation. The original CMC-Microbiology evaluation already captured and approved in the N213593MR01.doc, dated 01/13/2021. Hence, based on the above information the reviewer has concluded that the applicant has provided adequate information to support non-sterile manufacturing process of the drug product.

Acceptable

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:

Koushik Paul, Ph.D. and 05/16/2022

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Jesse Wells, Ph.D. and 05/16/2022



Jesse
Wells

Digitally signed by Jesse Wells

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Koushik
Paul

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RECOMMENDATION

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

NDA 213593

**KONVOMEF (Omeprazole and Sodium Bicarbonate for Oral Suspension)
Assessment #1**

Drug Product Name	KONVOMEF (omeprazole and sodium bicarbonate) for oral suspension
Dosage Form	For oral suspension
Strength	2 mg / 84 mg per mL The constituted suspension contains 2 mg/mL of omeprazole and 84 mg/mL of sodium bicarbonate
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Azurity Pharmaceuticals, Inc.
US agent, if applicable	Not Applicable

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission (0001)	03/30/2020	Drug Substance, Drug Product, OPMA, Biopharmaceutics, Micro, Labeling, EA Team
Amendment (0002)	04/15/2020	Labeling
Amendment (0003)	04/17/2020	Drug Substance, Drug Product, Biopharmaceutics, OPMA, Micro
Amendment (0007)	06/11/2020	Drug Substance, Biopharmaceutics, OPMA
Amendment (0008)	06/11/2020	Drug Product, OPMA, Micro
Amendment (0010)	07/02/2020	Drug Substance, Drug Product, OPMA, Micro
Amendment (0012)	08/04/2020	Micro
Amendment (0014)	08/27/2020	Drug Product, Biopharmaceutics
Amendment (0016)	09/15/2020	Drug Product
Amendment (0017)	09/03/2020	OPMA
Amendment (0019)	09/11/2020	Labels/labeling
Amendment (0020)	09/17/2020	OPMA, Micro
Amendment (0022)	09/21/2020	Drug Product
Amendment (0023)	09/28/2020	Drug Product
Amendment (0024)	09/25/2020	Biopharmaceutics, OPMA
Amendment (0025)	10/09/2020	Drug Product
Amendment (0026)	10/13/2020	Biopharmaceutics

Amendment (0027)	10/16/2020	Biopharmaceutics
Amendment (0028)	10/20/2020	Micro, OPMA
Amendment (0029)	10/28/2020	Micro
Amendment (0030)	10/30/2020	Drug Product, Micro
Amendment (0031)	11/20/2020	Drug Product
Amendment (0032)	12/04/2020	Drug Product, OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sukhamaya (Sam) Bain	Donna Christner
Drug Product	Mark Seggel	Wendy Wilson-Lee
Manufacturing	Mesfin Abdi	Yubing Tang
Microbiology	Alifiya Ghadiali	Samata Tiwari
Biopharmaceutics	Yang Zhao	Tapash Ghosh
Regulatory Business Process Manager	Marquita Burnett	
Application Technical Lead	Hong Cai, Ph.D.	
Laboratory (OTR)	-	-
Environmental	Mark Seggel	Wendy Wilson-Lee
Labeling	Mark Seggel	Wendy Wilson-Lee

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

As of this review, Azurity Pharmaceuticals 505(b)(2) New Drug Application #213593, for KONVOMEF (omeprazole and sodium bicarbonate) for oral suspension, 2 mg/84 mg per mL, is not ready for approval in its present form* per 21 CFR 314.125(b)(1) and (b)(8).

Based on our review of the chemistry, manufacturing, and controls information provided in the original submission and amendments listed as reviewed, we find that the proposed control strategy is insufficient to assure the identity, strength, purity, quality, and bioavailability of the drug product as required by 21 CFR 314.50. Specifically, the submission lacks sufficient information to demonstrate that the proposed control strategy for the omeprazole and sodium bicarbonate active pharmaceutical ingredients (APIs) of this combination product meets the regulatory standard.

The identity and strength of the API, sodium bicarbonate, in the drug product throughout the product shelf-life and during the in-use period is not adequately assured. (b) (4)

Further, the assay method for assuring the strength and uniformity of the API omeprazole in the constituted suspension at release and on stability is not adequately documented in the NDA.

From the drug product and the manufacturing process review perspectives, this application cannot be recommended for approval until adequate controls for the APIs, sodium bicarbonate and omeprazole, are established, and the applicant has demonstrated that drug product with the requisite quality can be manufactured consistently. See Attachment I of this review for a list of deficiencies to be conveyed to the applicant.

It is also recommended that, upon resubmission of the application, pre-approval inspections (PAI) of the relevant analytical testing laboratories of the diluent and constituted suspension be conducted.

Therefore, at this time, "the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability," (21 CFR 314.125(b)(1)).

Adequate drug substance, and product quality microbiology information has been provided. From the biopharmaceutics perspective, suitable controls for in vitro dissolution have been established.

The drug substance, drug product manufacturers and external testing facilities are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities to support this application at this time. However, the relevant facilities status will be reassessed at the time of the resubmission.

The labeling negotiations have not completed in this review cycle, and further review of labeling will be needed when the NDA is resubmitted. From the ONDP perspective, this application is not deemed ready for approval in its present form per 314.125(b)(8).

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(a) is acceptable.

**Note: The amendments dated December 15, 2020 (SN0033) and January 8, 2021 (SN0034 and SN0035), were not reviewed in the current review cycle.*

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This is a 505(b)(2) NDA application with the LDs, Zegerid® (omeprazole and sodium bicarbonate) for oral suspension (NDA 021636) and Prilosec® (omeprazole) delayed-released (DR) capsules (NDA 019810). The proposed indications for KONVOMEP in adults are for the treatment of (b) (4) treatment of active benign gastric ulcer;

(b) (4)

reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients.

KONVOMEP is a fixed-dose combination drug product containing two APIs. The API omeprazole which serves as a proton pump inhibitor (PPI) belongs to a class of antisecretory compounds with the substituted

benzimidazoles; the other API sodium bicarbonate which serves as an acid neutralizer is to prevent omeprazole degradation in the stomach and

(b) (4)

KONVOME[®]P is supplied as a multiple-unit kit containing one bottle of omeprazole powder, one bottle of matching diluent (strawberry-flavored) (b) (4). The bottle of omeprazole powder contains only the API omeprazole without any excipients. The diluent contains API sodium bicarbonate as a liquid, 84 mg/mL. (b) (4)

(b) (4). An oral dosing device to measure the desired dosing volume is not included in the kit.

(b) (4)

(b) (4). Prior to dispensing to patients, a pharmacist constitutes the oral suspension by adding the entire content of the diluent bottle to the bottle with omeprazole powder from the same kit. There are three package configurations for KONVOME[®]P, omeprazole powder as 0.18 g, 0.3 g or 0.6 g and the matching diluent as 90 mL, 150 mL, or 300 mL. When constituted, the concentrations of omeprazole and sodium bicarbonate are the same (2 mg omeprazole and 84 mg sodium bicarbonate per mL) in the suspension among the three packaging configurations (b) (4)

Azurity Pharmaceuticals, Inc., located at Wilmington, MA, USA, is the manufacturer for omeprazole component (packaging and release) and the secondary packager of the final KONVOME[®]P kit containing omeprazole bottles, the diluent bottles, package inserts (b) (4). The diluent bottles are manufactured by (b) (4).

Omeprazole is one of the most widely used PPIs to treat acid-mediated disorders such as GERD and peptic ulcer disease (PUD). KONVOME[®]P is a liquid formulation for patients, especially for the ones experiencing difficulty in swallowing tablets or capsules. The liquid formulation in general can offer flexible dosing. The strawberry flavor could improve the palatability of the formulation.

(b) (4)

(b) (4). Unlike the LD Zegerid for oral suspension which contains 1680 mg of sodium bicarbonate in both 40 mg or 20 mg of omeprazole unit dose packets, the amount of API sodium bicarbonate in KONVOME[®]P is

(b) (4)

(b) (4). Further, the API sodium bicarbonate is presented as a solution in KONVOME[®]P but as a solid in Zegerid until constitution.

The applicant is proposing to store the product at refrigerated, 2°C to 8°C (36°F to 46°F) with an expiration period of 24 months (from the date of manufacture of either the powder/diluent component whichever is earlier). The maximum patient use period is 30 days after the constitution when stored refrigerated.

Proposed Indication(s) including Intended Patient Population	• Short-term treatment of active benign gastric ulcer for 4 to 8 weeks • Reduction of risk of upper GI bleeding in critically ill adult patients
Duration of Treatment	
Maximum Daily Dose	40 mg daily (b) (4) daily (NG/OG)
Alternative Methods of Administration	NG/OG administration

B. Quality Assessment Overview

Drug Substance: Adequate

Omeprazole: The applicant has referenced (b) (4) for omeprazole drug substance CMC. The DMF has been found adequate to support approval of the NDA. Omeprazole used in the manufacture of the drug product conforms to the USP monograph for omeprazole and with ICH recommendations. The specifications established by the drug substance manufacturer and by the applicant provide assurance of the identity, strength, quality and purity of the drug substance.

The supplier (b) (4) has established a retest period of (b) (4) for omeprazole (b) (4)

Sodium Bicarbonate: The drug substance (b) (4)

(b) (4). The drug substance complies with the USP monograph for Sodium Bicarbonate, with additional satisfactory controls on elemental impurities and particle size distribution. (b) (4)
A retest period of (b) (4) months is granted when stored at (b) (4) RH. The supplier is (b) (4)
(b) (4)

The drug substance reviewer Dr. Sukhamaya (Sam) Bain finds the information on the drug substances omeprazole and sodium bicarbonate is adequate to support the approval of the NDA. See IQA Chapter Drug Substance for details.

Drug Product: Inadequate

KONVOMEF is a fixed-dose combination drug product containing two APIs: omeprazole and sodium bicarbonate. KONVOMEF is supplied as a kit containing one bottle of omeprazole powder, one bottle of matching diluent (strawberry-flavored) (b) (4). (b) (4)
(b) (4)

(b) (4) A pharmacist constitutes the oral suspension by adding the entire content in the diluent bottle to the matching bottle of omeprazole powder prior to dispensing to patients. There are three package configurations for KONVOMEF, omeprazole powder as 0.18 g, 0.3 g or 0.6 g and the matching diluent as 90 mL, 150 mL, or 300 mL. When constituted, the concentrations of omeprazole and sodium bicarbonate are the same (2 mg omeprazole and 84 mg sodium bicarbonate per mL) in the suspension among the three packaging configurations (b) (4)
(b) (4)

Both APIs, omeprazole and sodium bicarbonate, are compendial grade. The bottle of omeprazole powder contains only omeprazole with no excipients. The API, sodium bicarbonate, is contained in the diluent (strawberry-flavored) at a concentration of 84 mg/mL. In addition to sodium bicarbonate, the diluent contains the following excipients: benzyl alcohol (b) (4), FD&C Red No. 40 (b) (4) strawberry (Flavor), poloxamer 188 (b) (4) simethicone emulsion (b) (4) sodium citrate dihydrate (b) (4) sucralose (b) (4) sorbitol solution (b) (4) carboxymethylcellulose sodium (b) (4) and purified water. Except for FD&C Red No. 40 and the strawberry flavor, all the excipients are referenced to USP or NF. The (b) (4) FD&C Red No. 40 meets the quality standard per 21 CFR 74.1340. The strawberry flavor is supplied by (b) (4) and is described in Type IV DMF (b) (4) which was reviewed and found adequate by Dr. Kris Raman on August 18, 2014. The quality of the excipients including the flavoring (b) (4) are deemed adequate for the proposed drug product.

The applicant has proposed (b) (4)

The uniformity of dosage units per USP <905> and the microbial limits testing per USP <61> and <62> for oral product are added but some of the non-stability indicating tests, e.g. (b) (4) and residue on ignition are eliminated. It is considered adequate to ensure its identity, strength, purity and quality of the omeprazole component of the kit at release and throughout the shelf-life.

The proposed specifications for the diluent and the constituted oral suspension do not include testing and the acceptance criteria for the identity and strength of the API sodium bicarbonate. Although there is a test of the total sodium content, it is not deemed adequate to control the strength of sodium bicarbonate. Sodium ions are contributed from the excipient's sodium citrate and carboxymethylcellulose sodium in addition to sodium bicarbonate. Moreover, there are no data demonstrating that the diluent will consistently meet the requisite sodium bicarbonate assay acceptance criterion of (b) (4) % of the label claim at release and throughout the shelf-life. Similarly, there are no data to demonstrate that the constituted suspension will meet the 90.0% to 110.0% throughout the 30-day in-use period. Thus, the strength of the active ingredient, sodium bicarbonate, in the drug product throughout the product shelf-life and during the in-use period is not adequately assured. Further, the suitability of the proposed assay method sodium bicarbonate by (b) (4)

has not been fully demonstrated. Specifically, per method validation report (SGS-VAL-09-20-131R), (b) (4)

Thus, the obvious downward trending may result in the method underestimating the amount of sodium bicarbonate at the high end and, more importantly, may be overestimating the amount of sodium bicarbonate at the low end.

The strength and uniformity of the API omeprazole in the constituted suspension at release and on stability are not assured. The analytical procedure MET-CDM-000025 for omeprazole identification, assay, and within bottle uniformity, submitted October 16, 2020 (SN 0027) differs from the assay procedure (b) (4); submitted in 0001)) used for analyzing the constituted suspension in the registration stability studies. The analytical method validation report (04-R-MV-18-026.01) submitted in SN0001 does not cover the analytical procedure (b) (4). Additionally, the equivalence of MET-CDM-000025 to (b) (4) has not been demonstrated.

The container and closures are (b) (4) HDPE bottles supplied by (b) (4) with different child resistant caps with liners for both the diluent and the powder components. The applicant has performed the extractables screening (acidic and basic aqueous media (pH 3 and 11), and IPA:water (50:50, v/v)) and the leachables studies of the proposed (b) (4) HDPE bottles and the caps. Various analytical techniques were used to identify potential volatile, semi-volatile, non-volatile organic and elemental impurities. The pharm/tox reviewer, Dr. Kenrick Semple, has performed a safety assessment of the extractables and leachables study results and concluded there are no safety concerns regarding the use of the proposed container closure systems for the drug product. For details see his email communication dated on January 11, 2021.

Until complete batch data, including sodium bicarbonate assay, obtained at $t = 0$ and through at least $t = 6$ months storage under accelerated and long-term conditions, are available, it is premature to establish an expiration dating period for the product. Similarly, it is premature to make any conclusions regarding the in-use period without complete test data, including the sodium bicarbonate assay, covering the entire proposed in-use period, $t = 0$ to $t=30$ days.

Note that the results of in vitro testing of the physicochemical compatibility of the suspension with nasogastric/orogastric (NG/OG) tubes were not reviewed in this review cycle.

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(a). Dr. Seggel has accepted the applicant's request and has granted the categorical exclusion to this application.

In summary, Dr. Seggel has recommended a complete response for this application as per 21 CFR 314. 125 (b1) from the drug product perspective. It is also recommended that, upon resubmission of the application, pre-approval inspections (PAI) of the relevant analytical testing laboratories of the diluent and constituted suspension be conducted. See IQA Chapter II, Drug Product for details.

Labeling: Inadequate

The configuration of the kit presents the complexity with the nomenclatures of the proposed drug product, e.g. the product title presentation and the expression of the strength for each component bottle and the kit. The labeling review team (ONDP, OPPQ, DMEPA and the Clinical) has provided initial comments to the applicant via information

request on December 22, 2020. However, labeling negotiations have not completed in this review cycle.

Therefore, this application is not deemed ready for approval in its current form from ONDP perspective per 21 CFR 314.125(b)(8). Refer to IQA Labeling Chapter for details.

Manufacturing Integrated Assessment: Inadequate

(b) (4)

Facilities: adequate

The DS and DP manufacturers and external testing facilities are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities to support this application by the OPMA reviewer Dr. Mesfin Abdi.

See IQA OPMA Chapters for manufacturing process and the facilities for details.

Biopharmaceutics: Adequate

The Dissolution Method: The Biopharmaceutics information provided in this application has been reviewed by the biopharmaceutics reviewer, Dr. Yang Zhao who has recommended the approval of this application from biopharmaceutics perspective for the quality control. Overall, the Applicant has adequately established a suitable dissolution test method

and acceptance criterion (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4 with the dissolution acceptance criterion “Q = (b) (4) % at 30 min”) to ensure the quality and bioavailability of KONVOME[®]P (omeprazole and sodium bicarbonate) for oral suspension.

(b) (4) The Applicant conducted a relative bioavailability study of a single dose of KONVOME[®]P, 40 mg/1680 mg vs. the LD, Zegerid[®], 40 mg/1680 mg. (b) (4)

See IQA Biopharmaceutics Chapter for details.

Microbiology (if applicable): Adequate

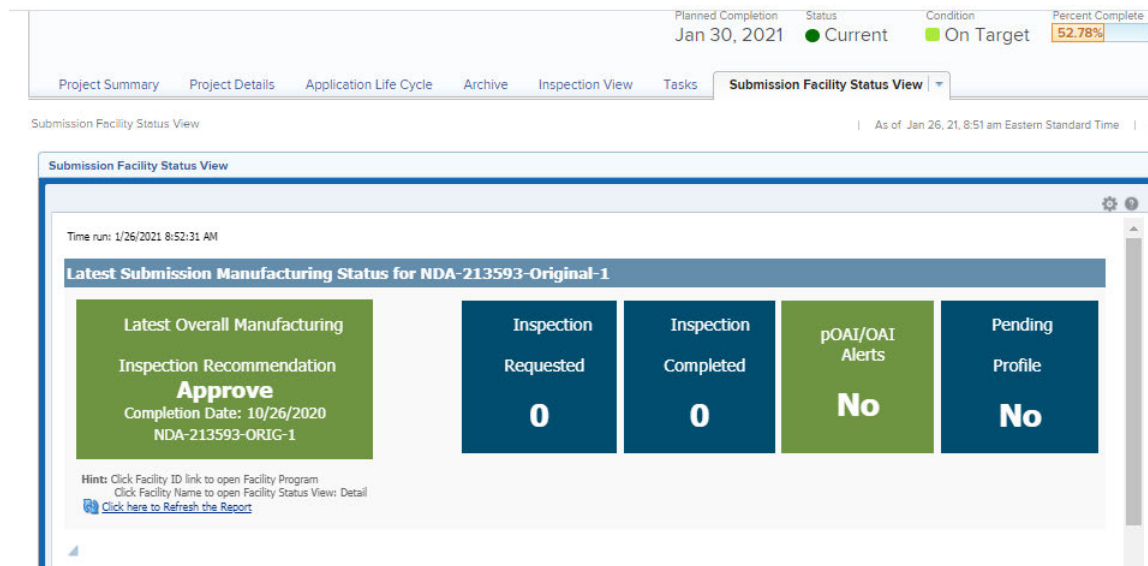
KONVOME[®]P is a non-sterile drug product with omeprazole as a (b) (4) powder, and the diluent and the constituted suspension as liquids. The diluent contains benzyl alcohol (b) (4). The applicant has provided the microbial limits testing of TAMC and TYMC per USP<61> and E. coli per USP<62> in omeprazole powder component release and stability specification. The testing of the benzyl alcohol assay, microbial limits of TAMC and TYMC per USP <61> and E. Coli per USP <62> and BCC per USP <60> are part of the diluent and the constituted suspension specification. Additionally, Antimicrobial Effectiveness Testing (AET) per USP <51> is included in the specification of the constituted suspension. The overall manufacturing and the environmental monitoring, along with appropriate testing, provide assurance of acceptable microbiological quality of the drug product.

The microbiology data is adequate to support a 24 months shelf-life of kit components when stored at 2-8°C. Further, the Applicant has provided sufficient AET data to support the proposed post-constitution storage time of 30 days at 2-8°C (proposed patient in-use period).

The microbiology information submitted in this application has been reviewed by the microbiology reviewer Dr. Alifiya Ghadiali who has found the information provided in the application adequate to support the approval of this application from the microbiology perspective. See the detailed review from Dr. Ghadiali in the Microbiology Chapter of the IQA.

FACILITY STATUS REPORT AND OVERALL RECOMMENDATION

The drug substance, drug product manufacturers and external testing facilities are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities to support this application at this time (See the screen capture of the “Submission facility Status View” from Panorama). However, the relevant facilities status will be reassessed at the time of the resubmission.



C. Risk Assessment

A Final Risk Assessment with Lifecycle Considerations will be completed following resubmission of this NDA.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

na

2. Drug Substance Deficiencies

na

3. Drug Product Deficiencies

1. The strength of the active ingredient, sodium bicarbonate, in the drug product throughout the product shelf-life and during the in-use period is not adequately assured.

- a. The suitability of proposed assay method for the active ingredient sodium bicarbonate (b) (4)

has not been fully

demonstrated. Specifically, (b) (4)

(b) (4)

- b.

(b) (4)

2. The strength and uniformity of the active ingredient omeprazole in the constituted suspension at release and on stability are not assured. Analytical procedure MET-CDM-000025 for omeprazole identification, assay, and within bottle uniformity, submitted on October 16, 2020 (SN 0027) differs from the assay procedure (b) (4) submitted in SN 0001)) used for analyzing the constituted suspension in the registration stability studies. Furthermore, the Analytical Method Validation Report (04-R-MV-18-026.01) submitted in SN0001 does not cover Method (b) (4). Additionally, the comparability of MET-CDM-000025 to (b) (4) has not been demonstrated.

4. Labeling Deficiencies

Labeling negotiation has not been completed. The initial comments were sent to the Applicant on December 22, 2020 (See DARRTS). No additional comments being conveyed at this time.

5. Manufacturing Deficiencies

You have not established an in-process control (b) (4)
(b) (4)
(b) (4)

6. Biopharmaceutics Deficiencies

na

7. Microbiology Deficiencies

na

8. Other Deficiencies (Specify discipline, such as Environmental)

na

Application Technical Lead Name and Date:

Hong Cai, Ph.D.
CMC Lead (acting)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	08/28/2020	See IQA Chapter 1, Drug Substance for additional information
	IV			Adequate	08/18/2014	See IQA Drug Product Chapter for additional information
	III			NA		
	III			NA		
	III			NA		
	III			NA		
	III			NA		
	III			NA		

N/A: There is enough data in the application, therefore the DMF did not need to be reviewed during the current review cycle.

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

Document	Application Number	Description
IND submissions, associated reviews, and communications	IND 126863	Investigational use of omeprazole and sodium bicarbonate for oral suspension
NDA application(s) as the Listed Drugs	NDA 021636 NDA 019810	Zegerid® (omeprazole and sodium bicarbonate) for oral suspension Prilosec® (omeprazole) delayed-release capsules

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH-ODE	na			
CDRH-OC	na			
Clinical	na			
Other	na			



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CHAPTER IV: LABELING

[\(Refer to the IQA NDA Assessment Guide Reference\)](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

This assessment is based on the proposed Prescribing Information (PI) submitted on April 15, 2020 (SN002).

Konvomep is a fixed-combination drug product containing two active pharmaceutical ingredients (APIs), omeprazole and sodium bicarbonate, but it is supplied as a Kit, with omeprazole powder in one bottle and the diluent, which contains sodium bicarbonate, in the other bottle. Prior to dispensing, a pharmacist adds the content of the diluent/sodium bicarbonate bottle to the bottle of omeprazole powder. The constituted suspension is dispensed and stored (for up to 30-days – the proposed patient in-use period) in the omeprazole powder bottle. The configuration of the kit presents unique labeling issues related to nomenclature, product title presentation, and expression of strength, of the kit and individual components. The labeling review team (ONDP, OPPQ, DMEPA and clinical) provided initial comments to the applicant in a December 22, 2020 information request. However, labeling negotiations will not be completed in the current review cycle.

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Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	KONVOMEP	Satisfactory
Established name(s)	(omeprazole/sodium bicarbonate) for Oral Suspension	Not Satisfactory Revise (b) (4) to “(omeprazole and sodium bicarbonate)”
Route(s) of administration	Oral	Satisfactory
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Not Satisfactory Revise to: “For Oral Suspension: 2 mg omeprazole and 84 mg sodium bicarbonate per mL after reconstitution in 90 mL, 150 mL, or 300 mL bottles.”
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	na	
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.	na	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)



Item	Information Provided in the NDA	Assessor's Comments
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)	See proposed Section "2.3 Preparation and Administration" copied from the proposed PI.	Satisfactory* *Refer to the additional comments from the clinical review team in the information request dated December 22, 2020 in DARRTS.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)



(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4) for oral suspension	Not Satisfactory The dosage form is "for oral suspension"
Strength(s) in metric system	2 mg/mL omeprazole and 84 mg/mL sodium bicarbonate	Satisfactory
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	na	na
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Not provided	Not Satisfactory Add in the description of the identifying characteristics of the dosage form. Revise to: For Oral Suspension: 2 mg omeprazole and 84 mg sodium bicarbonate per mL of a pink to red hazy, strawberry-flavored liquid after reconstitution in 90 mL, 150 mL, or 300 mL bottles. Each kit contains a bottle of omeprazole as a white to off-white powder and a strawberry-flavored diluent containing sodium bicarbonate as a slightly hazy red liquid [see Description (11) and How Supplied/Storage and Handling (16)]
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	na	na

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	na	na
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1.2.3 Section 11 (DESCRIPTION)

(b) (4)



Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	KONVOMEF (omeprazole/sodium bicarbonate) for Oral Suspension	Not Satisfactory Revise to KONVOMEF (omeprazole and sodium bicarbonate) for oral Suspension
Dosage form(s) and route(s) of administration	for Oral Suspension	Satisfactory
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	na	na
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The Strawberry-Flavored Diluent contains sodium bicarbonate and the following inactive ingredients: strawberry flavor, benzyl alcohol, FD&C red No. 40, poloxamer 188, carboxymethylcellulose sodium, purified water, simethicone emulsion, sodium citrate (dihydrate), sorbitol solution and sucralose.	Not Satisfactory Revise "FD&C red No. 40" to "FD&C Red No. 40", "strawberry flavor" to "strawberry flavor (natural and artificial flavors, propylene glycol, and glycerin)"
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.	Information of pH is not provided	Not Satisfactory Provide the pH information of the formulation.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	na	na
Statement of being sterile (if applicable)	na	na

Pharmacological/therapeutic class	omeprazole, a proton pump inhibitor, and sodium bicarbonate, an antacid.	Satisfactory
Chemical name, structural formula, molecular weight	Information for sodium bicarbonate is not provided.	Not Satisfactory Add the following information for sodium bicarbonate: The molecular formula is NaHCO ₃ and the molecular weight is 84.01. The structural formula is: $^+\text{Na}^-\text{O}-\text{C}(=\text{O})-\text{OH}$
If radioactive, statement of important nuclear characteristics.	na	na
Other important chemical or physical properties (such as pKa or pH)	Information for sodium bicarbonate is not provided.	Add the following for sodium bicarbonate: "Sodium bicarbonate is a white crystalline powder. It is soluble in water and insoluble in alcohol. One gram of sodium bicarbonate dissolves in 12 ml of water at 25°C. The pH of a freshly prepared 0.1 molar aqueous solution is 8.3 at 25°C. Aqueous solutions slowly convert to sodium carbonate through loss of carbon dioxide."

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	na	na

Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	na	na
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1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments												
HOW SUPPLIED/STORAGE AND HANDLING section														
Available dosage form(s)	for oral suspension	Not Satisfactory												
Strength(s) in metric system	in the strengths and volumes listed in Table 2.	Not Satisfactory												
Available units (e.g., bottles of 100 tablets)	90 mL KONVOMEK kit 150 mL KONVOMEK kit 300 mL KONVOMEK kit	Satisfactory												
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) (b) (4) one bottle of omeprazole USP, a white to off-white powder (b) (4) and one bottle of pre-measured Strawberry-Flavored Diluent containing sodium bicarbonate	Not Satisfactory Revise to: TRADENAME (omeprazole and sodium bicarbonate) for oral suspension 2 mg/84 mg per mL is supplied as: A kit containing one bottle of omeprazole USP, a white to off-white powder and one bottle of pre-measured strawberry-flavored Diluent containing sodium bicarbonate, (b) (4) (see table below). <table border="1"> <thead> <tr> <th>NDC Number</th><th>Total Volume after reconstitution</th><th>Kit Contents</th></tr> </thead> <tbody> <tr> <td>85024-270-01</td><td>90 mL</td><td>Bottle of 180 mg omeprazole powder and a bottle of diluent containing sodium bicarbonate 7.58 g per 90 mL.</td></tr> <tr> <td>85024-270-01</td><td>150 mL</td><td>Bottle of 300 mg omeprazole powder and a bottle of diluent containing sodium bicarbonate 12.6 g per 150 mL.</td></tr> <tr> <td>85024-270-10</td><td>300 mL</td><td>Bottle of 600 mg omeprazole powder and a bottle of diluent containing sodium bicarbonate 25.2 g per 300 mL.</td></tr> </tbody> </table>	NDC Number	Total Volume after reconstitution	Kit Contents	85024-270-01	90 mL	Bottle of 180 mg omeprazole powder and a bottle of diluent containing sodium bicarbonate 7.58 g per 90 mL.	85024-270-01	150 mL	Bottle of 300 mg omeprazole powder and a bottle of diluent containing sodium bicarbonate 12.6 g per 150 mL.	85024-270-10	300 mL	Bottle of 600 mg omeprazole powder and a bottle of diluent containing sodium bicarbonate 25.2 g per 300 mL.
NDC Number	Total Volume after reconstitution	Kit Contents												
85024-270-01	90 mL	Bottle of 180 mg omeprazole powder and a bottle of diluent containing sodium bicarbonate 7.58 g per 90 mL.												
85024-270-01	150 mL	Bottle of 300 mg omeprazole powder and a bottle of diluent containing sodium bicarbonate 12.6 g per 150 mL.												
85024-270-10	300 mL	Bottle of 600 mg omeprazole powder and a bottle of diluent containing sodium bicarbonate 25.2 g per 300 mL.												
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	na	na												
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.	na	na												

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	Keep containers tightly closed.	Satisfactory
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	na	na
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store KONVOMEK kit in the refrigerator, 2° to 8°C (36° to 46°F). Store reconstituted suspension of KONVOMEK in the refrigerator, 2° to 8°C (36° to 46°F). (b) (4)	Not satisfactory Revise "Discard (b) (4) Suspension after 30 days." to "Discard KONVOMEK oral suspension after 30 days."
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: "Not made with natural rubber latex. Avoid statements such as "latex-free."	na	na
Include information about child-resistant packaging		

1.2.5 Other Sections of Labeling

Assessment: The drug product (diluent/constituted suspension) contains (b) benzyl alcohol (b) (4). Because there are potential safety issues associated with benzyl alcohol, appropriate warnings and precautions may be warranted (see Labeling Review Tool (LRT), Sept. 2019). Although the safety issues are of particular concern for IV products administered to neonates and infants, particularly when administered to neonates and infants, and Konvomep is intended for oral administration to adults, the LRT does not distinguish routes of administration or patient population. The CMC review team will defer to clinical to determine what is appropriate for this product labeling.

Because control of total sodium intake may be critical for some patients, the labeling will include total sodium as mg/mL (derived from sodium bicarbonate, sodium citrate and carboxymethylcellulose sodium).

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: Azurity Pharmaceuticals, Inc. Wilmington, MA 01887 USA	Satisfactory

2.0 PATIENT LABELING

Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Not assessed in this review cycle.

8 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	<i>Omeprazole Powder Bottles:</i> TRADENAME <i>(omeprazole/sodium bicarbonate)</i> <i>For Oral Suspension</i> <i>Diluent Bottles:</i> DILUENT <i>for reconstitution of TRADENAME</i> <i>(omeprazole/sodium bicarbonate)</i> <i>for Oral Suspension</i> <i>Kits:</i> TRADENAME <i>(omeprazole/sodium bicarbonate)</i> <i>for Oral Suspension</i>	Not Satisfactory 1. Replace the slash '/' between active ingredient names with the word 'and.' For example, (omeprazole/sodium bicarbonate) becomes (omeprazole and sodium bicarbonate). 2. Revise the dosage form to 'for oral suspension.' <i>Diluent Bottles:</i> 1. Replace 'DILUENT for reconstitution of' with 'DILUENT for.' 2. Place the statement, 'CONTAINS: sodium bicarbonate, USP, 84 mg/mL' directly below the product title. <i>Kits:</i>

Dosage strength	<i>Omeprazole Powder Bottles:</i> When reconstituted, each mL contains 2 mg Omeprazole USP and 84 mg Sodium Bicarbonate USP. <i>Diluent Bottles:</i> CONTAINS: Sodium Bicarbonate USP 84 mg/mL. <i>Kits:</i> 2 mg/84 mg	Not Satisfactory <i>Omeprazole Powder Bottles:</i> Add the following expression of strength below the product title: 2mg/84 mg per mL* Revise the statement, 'When reconstituted, each mL contains 2 mg Omeprazole USP and 84 mg Sodium Bicarbonate USP' to '*When reconstituted, each mL contains 2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP.' <i>Kits:</i> Add the following expression of strength below the product title: 2mg/84 mg per mL* On the carton PDP, revise 'When reconstituted, each mL contains 2 mg Omeprazole USP and 84 mg Sodium Bicarbonate USP' to '*When reconstituted, each mL contains 2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP.'
Route of administration	for Oral Suspension	Satisfactory
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	na	na

Net contents (e.g. tablet count)	• <i>Omeprazole Powder Bottles:</i> e.g. <i>This bottle contains 0.6 g of Omeprazole Powder.</i> • <i>Diluent Bottles:</i> e.g. <i>Net Contents 300 mL</i> • <i>Kits:</i> e.g. <i>300 mL final volume after reconstitution.</i>	Not Satisfactory • <i>Diluent Bottles:</i> Revise the Net Content statement to 'Net Contents X g sodium bicarbonate in Y mL.' • <i>Kits</i> 1. Under, 'Each Kit Includes:' revise • One bottle containing XX g Omeprazole Powder • One bottle containing Y mL Strawberry-Flavored Diluent to • One bottle containing XX g omeprazole powder • One bottle containing X g sodium bicarbonate in Y mL strawberry-flavored Diluent 2. Revise 'Strawberry-Flavored Diluent,' to either 'Diluent' or 'strawberry-flavored Diluent.'
"Rx only" displayed on the principal display	• <i>Omeprazole Powder Bottles: provided</i> • <i>Diluent Bottles: provided</i> • <i>Kits: provided</i>	Satisfactory
NDC number	• <i>Omeprazole Powder Bottles: provided</i> • <i>Diluent Bottles: not provided</i> • <i>Kits: provided</i>	Satisfactory
Lot number and expiration date	Lot: XXXXX Exp: MM/YYYY	Satisfactory

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	• <i>Omeprazole Powder Bottles:</i> (b) (4) (2°C-8°C/36°F-46°F) • <i>Diluent Bottles:</i> • <i>Kits:</i> • Store refrigerated (2°– 8°C / 36°– 46°F) • (b) (4)	Not Satisfactory • <i>Omeprazole Powder Bottle:</i> Replace the storage statement, (b) (4) (2°C-8°C/36°F-46°F)' with either, Store in a refrigerator, 2°C to 8°C (36°F to 46°F) or Store refrigerated, 2°C to 8°C (36°F to 46°F) • <i>Diluent Bottles:</i> • <i>Kits:</i> Storage condition presentation should be consistent for main and side panels.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	na	na
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	na	na
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	na	na
Bar code	provided	Satisfactory

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Kits: Manufactured by AZURITY pharmaceuticals Wilmington, MA 01887 USA	Satisfactory
Medication Guide (if applicable)	na	na
No text on Ferrule and Cap overseal	na	na
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.	na	na
And others, if space is available		

Assessment of Carton and Container Labeling: *Inadequate.*

Konvomep contains two APIs, omeprazole and sodium bicarbonate, but in separate bottles in the kit. Further, the constituted suspension will be contained in the bottle for the omeprazole powder. The recommended product title, strength and the net content expression is based on the agreement among labeling review team (ONDP, OPPQ, DMEPA and clinical). Refer to the initial comments to the applicant on December 22, 2020 information request in DARRTS. However, labeling negotiations have not completed in this review cycle.

ITEMS FOR ADDITIONAL ASSESSMENT

na

List of deficiencies from initial assessments:

A. Prescribing Information:

1. Replace the slash in the established name '/' between active ingredient names with the word 'and.' For example, (omeprazole/sodium bicarbonate) becomes (omeprazole and sodium bicarbonate).
2. The dosage form is "for oral suspension".
3. The strength should be expressed as per mL.
4. Revise "Section 3 Dosage Forms and Strengths" to the following: "For Oral Suspension: 2 mg omeprazole and 84 mg sodium bicarbonate per mL of a pink to red hazy, strawberry-flavored liquid after reconstitution in 90 mL, 150 mL, or 300 mL bottles. Each kit contains a bottle of omeprazole as a white to off-white powder and a strawberry-flavored diluent containing sodium bicarbonate as a slightly hazy red liquid [see Description (11) and How Supplied/Storage and Handling (16)]"
5. In Section 11 Description:
 - a. Add the function of sodium bicarbonate into as the following: "Sodium bicarbonate raises the gastric pH and protects the omeprazole from acid degradation."
 - b. Add the physical and chemical description and the chemical structural information of sodium bicarbonate into Section 11 Description.
 - c. Revise the name of the inactive ingredient from "strawberry flavor" to "strawberry flavor (natural and artificial flavors, propylene glycol, and glycerin)". Revise "FD&C red No. 40" to "FD&C Red No. 40".
 - d. Remove "equivalent to 1 mEq/mL of sodium)".
 - e. Add the following table:

Table 7: TRADENAME Contents

<u>Suspension Volume (as Dispensed)</u>	<u>Bottle of Omeprazole Powder</u>	<u>Bottle of Diluent Containing Sodium Bicarbonate</u>
<u>90 mL</u>	<u>180 mg</u>	<u>7.56 g per 90 mL</u>
<u>150 mL</u>	<u>300 mg</u>	<u>12.6 g per 150 mL</u>
<u>300 mL</u>	<u>600 mg</u>	<u>25.2 g per 300 mL</u>

6. In Section 16 How Supplied/Storage And Handling, add the identification characteristics and the strength of the drug product.

B. Carton and Container Labels:

1. General Comments (applicable to all labels)
 - a. Replace the slash '/' between active ingredient names with the word 'and.' For example, (omeprazole/sodium bicarbonate) becomes (omeprazole and sodium bicarbonate).
 - b. Revise the dosage form to 'for oral suspension.'
 - c. Replace the storage statement, (b) (4) (2°C-8°C/36°F-46°F)

with either,

Store in a refrigerator, 2°C to 8°C (36°F to 46°F)

or

Store refrigerated, 2°C to 8°C (36°F to 46°F)

Delete the note '[see (b) (4)]' from the storage statement.

2. Omeprazole Bottle Labels

a. Add the following expression of strength below the product title:

2 mg/84 mg per mL*

b. Revise the statement, 'When reconstituted, each mL contains 2 mg Omeprazole USP and 84 mg Sodium Bicarbonate USP' to '*When reconstituted, each mL contains 2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP.'

3. Diluent Bottle Labels

a. Replace 'DILUENT for (b) (4)' with 'DILUENT for.'

b. Place the statement, 'CONTAINS: sodium bicarbonate, USP, 84 mg/mL' directly below the product title.

c. Revise 'Powder' to 'powder.'

d. Revise the Net Content statement to 'Net Contents X g sodium bicarbonate in Y mL.'

4. Kit Carton Labels

a. Add the following expression of strength below the product title:

2 mg/84 mg per mL*

b. On the carton PDP, revise 'When reconstituted, each mL contains 2 mg Omeprazole USP and 84 mg Sodium Bicarbonate USP' to '*When reconstituted, each mL contains 2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP.'

c. Under, 'Each Kit Includes:' revise

- One bottle containing XX g Omeprazole Powder
- One bottle containing Y mL Strawberry-Flavored Diluent

to

- One bottle containing XX g omeprazole powder
 - One bottle containing X g sodium bicarbonate in Y mL strawberry-flavored Diluent
- d. Revise 'Strawberry-Flavored Diluent,' to either 'Diluent' or 'strawberry-flavored Diluent.'

Overall Assessment and Recommendation:

The labeling negotiations have not completed in this review cycle. From the ONDP perspective, this application is *not* deemed ready for approval in its present form per 314.125(b)(8).

Primary Labeling Assessor Name and Date:

Mark R. Seggel, January 22, 2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson-Lee, Ph.D.



Mark
Seggel

Digitally signed by Mark Seggel

Date: 1/23/2021 04:03:22PM

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Wendy
Wilson- Lee

Digitally signed by Wendy Wilson- Lee

Date: 1/25/2021 11:58:13AM

GUID: 50816dbc000085595ca3284bbca465a8

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BIOPHARMACEUTICS**NDA:** 213593

Drug Product Name/Strength: Omeprazole for Oral Suspension Kit (to be reconstituted with pre-measured Strawberry-Flavored Diluent to a suspension with omeprazole concentration of 2 mg/mL)/Three configurations of 90 mL, 150 mL, and 300 mL

Route of Administration: Oral

Applicant Name: Azurity Pharmaceuticals Inc.

List of Reviewed Submissions:

Original NDA 213593 submission dated 03/30/2020

Response dated 06/11/2020 to the Information Request dated 05/12/2020

Response dated 08/27/2020 to the Information Request dated 07/27/2020

Response dated 09/25/2020 to the Information Request dated 09/18/2020

Response dated 10/08/2020 to the Information Request dated 10/06/2020

Biopharmaceutics Review Team:

Primary Reviewer: Yang Zhao, Ph.D.

Secondary Reviewer: Tapash Ghosh, Ph.D.

REVIEW SUMMARY:

Azurity Pharmaceuticals Inc. submitted NDA 213593 seeking approval for Omeprazole for Oral Suspension kit under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4)

(b) (4) treatment of active benign gastric ulcer, (b) (4)

(b) (4) and reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients.

Review Objective: The Biopharmaceutics Review evaluated the adequacy of the proposed dissolution method and acceptance criterion for QC testing of the proposed drug product at batch release and during stability.

Reviewer's Assessment:**(1) Dissolution Method:**

The Applicant originally proposed "USP 2 at (b) (4) in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4 at 37 °C" as dissolution method for the batch release and stability testing for the proposed Omeprazole for Oral Suspension. (b) (4)

(b) (4)

(b) (4)

(2) Dissolution Acceptance Criterion:

Based primarily on the provided dissolution data of clinical batch and registration batches, the dissolution acceptance criterion of “Q = (b) (4)% at 30 min” is acceptable.

OVERALL RECOMMENDATION:

From the Biopharmaceutics perspective, the provided information and data are adequate and NDA 213593 for Omeprazole for Oral Suspension Kit is recommended for **APPROVAL**.

The FDA-approved dissolution method and acceptance criterion for the proposed Omeprazole for Oral Suspension Kit are:

Final Dissolution Method and Acceptance Criterion for Omeprazole for Oral Suspension Kit				
USP Apparatus	Speed (rpm)	Medium/Temp	Volume (mL)	Acceptance Criterion
USP 2 (paddle)	25	0.25 mM sodium phosphate buffer, pH 7.4/37 °C	900	Q = (b) (4)% at 30 minutes

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND OF THE PROPOSED DRUG PRODUCT:**1.1 Listed Drug:**

The proposed drug product is submitted as a 505(b)(2) and the Listed Drug (LD) is Zegerid (omeprazole) Powder for Oral Suspension (NDA-21636, approved by FDA on 06/15/2004). The Applicant conducted a relative bioavailability study comparing the proposed product vs. LD (Study OME-RM02-001).

1.2 Solubility and stability of omeprazole API:

In the provided dissolution method development report¹, the Applicant reported the solubility of omeprazole in pHs (0.22 mg/mL in pH 6.8 and 0.195 mg/mL in pH 7.4 at 25 °C). Additionally, this Reviewer located omeprazole aqueous solubility data in Module 3.2.S (0.0046, 0.0068, 0.026, 0.105, 0.025, 0.037, and 0.2 mg/mL in pHs 1, 2, 3, 4, 7, 8, and 10, respectively) and observed the

(b) (4)

(b) (4)

1.3 Configurations:

Each Omeprazole for Oral Suspension kit contains 1 bottle of omeprazole powder component and 1 bottle of pre-measured Strawberry-Flavored Diluent, containing sodium bicarbonate. The proposed product has three configurations (Table 1). Three configurations include omeprazole for oral suspension, 180 mg, 300 mg, and 600 mg; and Strawberry-Flavored Diluent, 90 mL, 150 mL

¹ \\cdsesub1\evsprod\nda213593\0007\m3\32-body-data\32p-drug-prod\omeprazole-for-oral-susp-oral-suspension-azurity-pharmaceuticals\32p2-pharm-dev\pharmaceutical-development-2.pdf

or 300 mL, respectively. For administration, per proposed labeling, a healthcare provider must reconstitute omeprazole powder with the Strawberry-Flavored Diluent. The reconstituted suspension from each configuration contains 2 mg/mL of omeprazole and 84 mg/mL of sodium bicarbonate. Per Applicant's proposed labeling, the recommended dose is [REDACTED] 40 mg (20 mL).

Table 1. Omeprazole for Oral Suspension kit configuration

1.4 Components of the drug product:

The Applicant reported that the bottle of Omeprazole USP powder [REDACTED].

The bottle of Strawberry-Flavored Diluent contains sodium bicarbonate, compendial excipients [benzyl alcohol [REDACTED] carboxymethylcellulose sodium [REDACTED], poloxamer 188 as [REDACTED] simethicone emulsion [REDACTED] sodium citrate (dihydrate) [REDACTED] sorbitol and sucralose [REDACTED], purified water [REDACTED] and noncompendial excipients (FD&C Red No. 40 [REDACTED] [REDACTED]). The primary purpose of sodium bicarbonate, [REDACTED] protect omeprazole from [REDACTED] acid degradation. Sodium citrate [REDACTED] [REDACTED]. The diluent and constituted drug product are formulated to a target pH of 9 (range of [REDACTED]).

Per the proposed labeling, Omeprazole Oral Suspension [REDACTED].

2. PROPOSED DISSOLUTION METHOD AND ACCEPTANCE CRITERION:

The proposed dissolution method and dissolution acceptance criterion for Omeprazole for Oral Suspension are as follows:

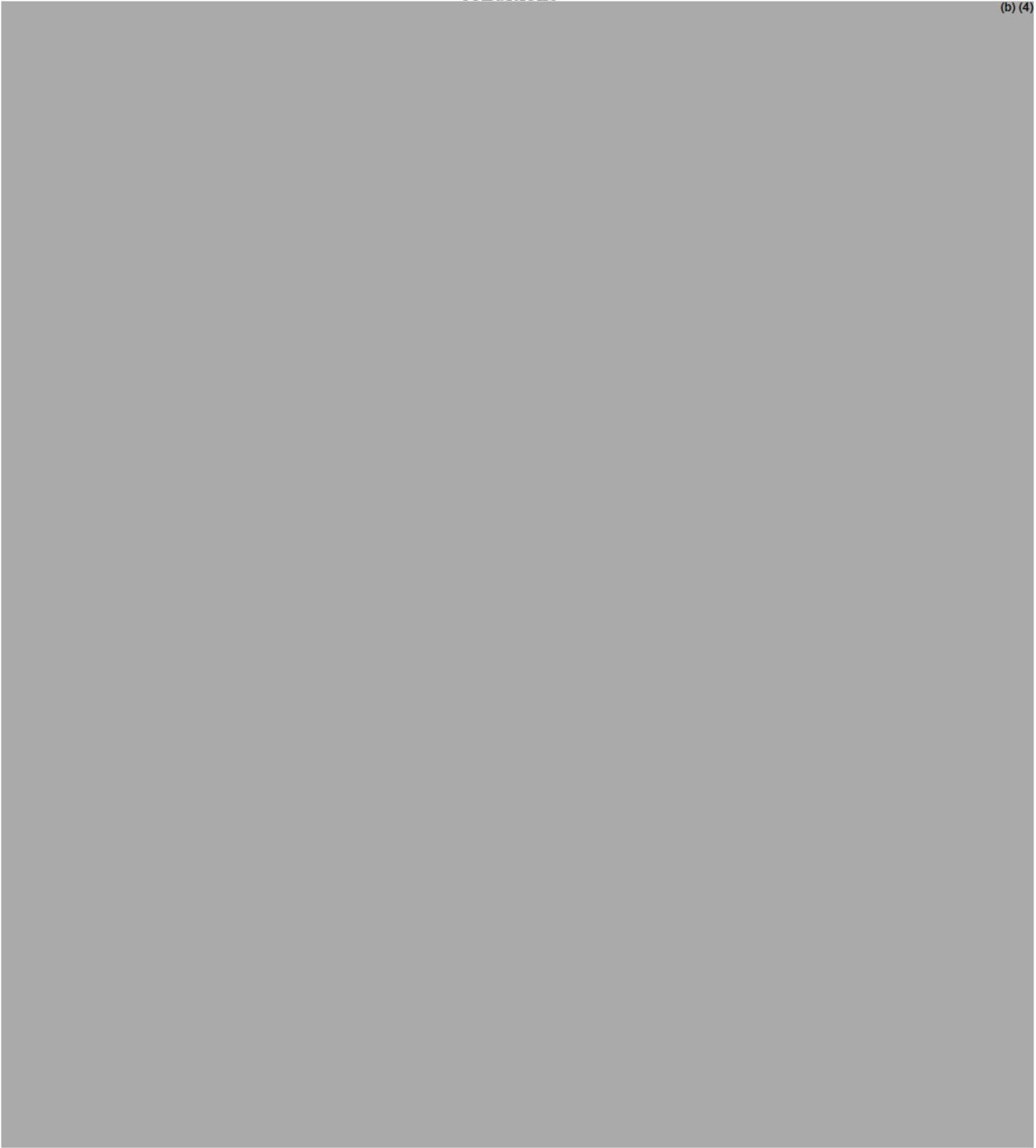
Proposed dissolution method and acceptance criterion for Omeprazole for Oral Suspension				
USP Apparatus	Speed	Medium/Temp	Volume (mL)	Acceptance Criterion
USP 2 (paddle)	(b) rpm	0.25 mM sodium phosphate buffer solution, pH 7.4/37 °C	900	Q = (b) % at 30 minutes

For the dissolution data obtained for the registration batches, [REDACTED] suspension volume was used in dissolution testing.

(b) (4)

Table 2. Dissolution profile data for Omeprazole Oral Suspension using different dissolution conditions

(b) (4)



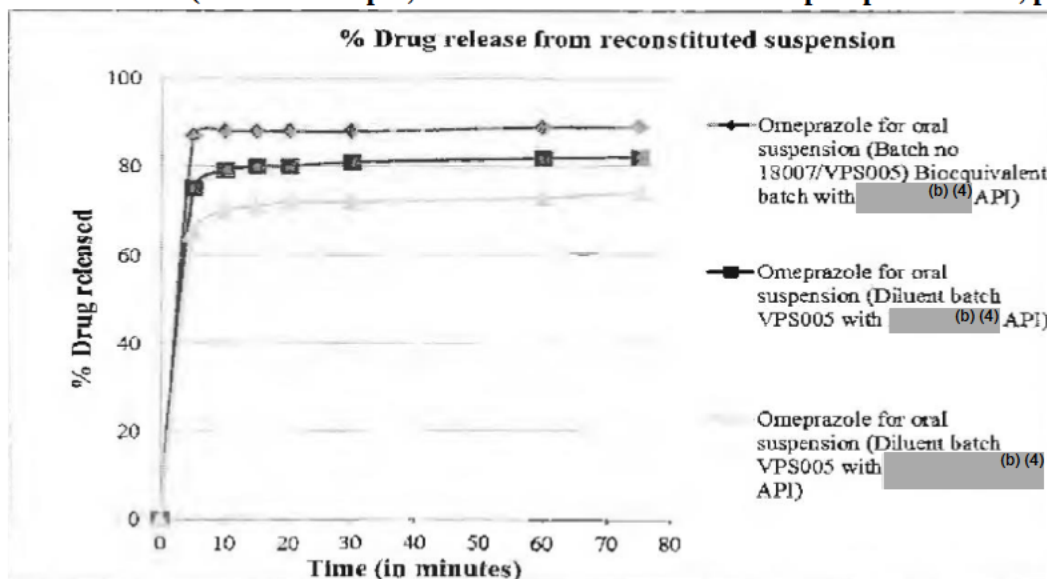
2.2 Evaluation of discriminating ability for the method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4):

In the original submission, the Applicant did not demonstrate any discriminating ability data. In the Information Request dated 07/27/2020, the Applicant was requested to provide data supporting the potential discriminating ability for the dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4).

In the response dated 09/25/2020, the Applicant provided data for evaluation of the discriminating ability for the dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4) for the proposed Omeprazole for Oral Suspension².

The Applicant used (b) (4) API for the manufacturing of the proposed Omeprazole for Oral Suspension and the API particle size specification is D₁₀: NMT (b) (4) D₅₀: NMT (b) (4) and D₉₀: NMT (b) (4). In the Response dated 09/25/2020, the Applicant provided dissolution data from batches manufactured with (b) (4) API (with particle size distribution: D₁₀: (b) (4), D₅₀: (b) (4) and D₉₀: (b) (4)). The dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4) was discriminating towards the changes in (b) (4) API with similarity factor, $f_2=39$ (Figure 1).

Figure 1. Impacts of API particle size on dissolution of Omeprazole for Oral Suspension using the dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4)

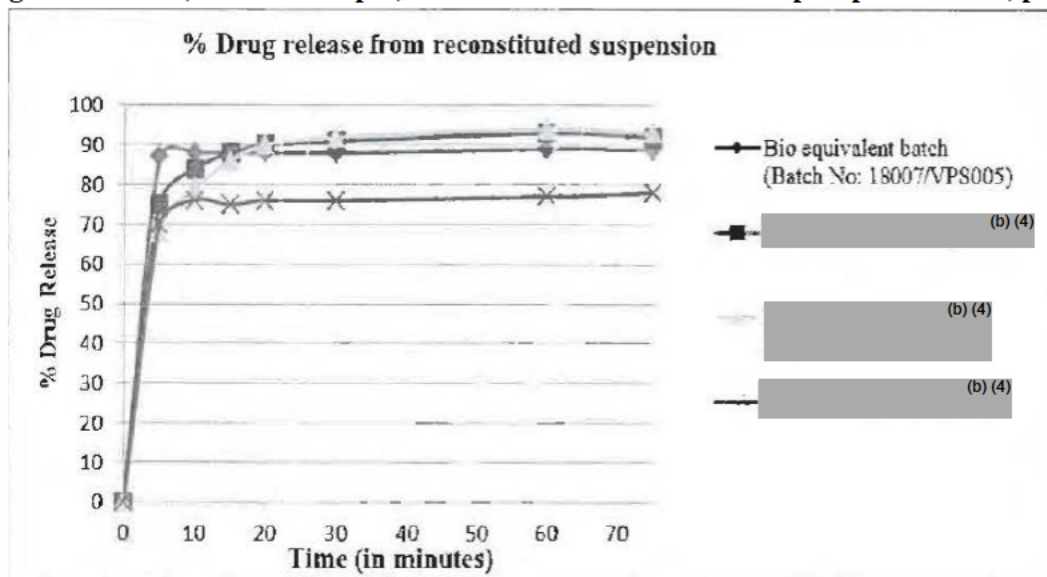


The dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4) was shown to be discriminating towards the changes in the amounts of (b) (4) (Figure 2).

² \\CDSESUB1\evsprod\nda213593\0024\m1\us\111-information-amendment\quality-information-amendment-sn0024.pdf

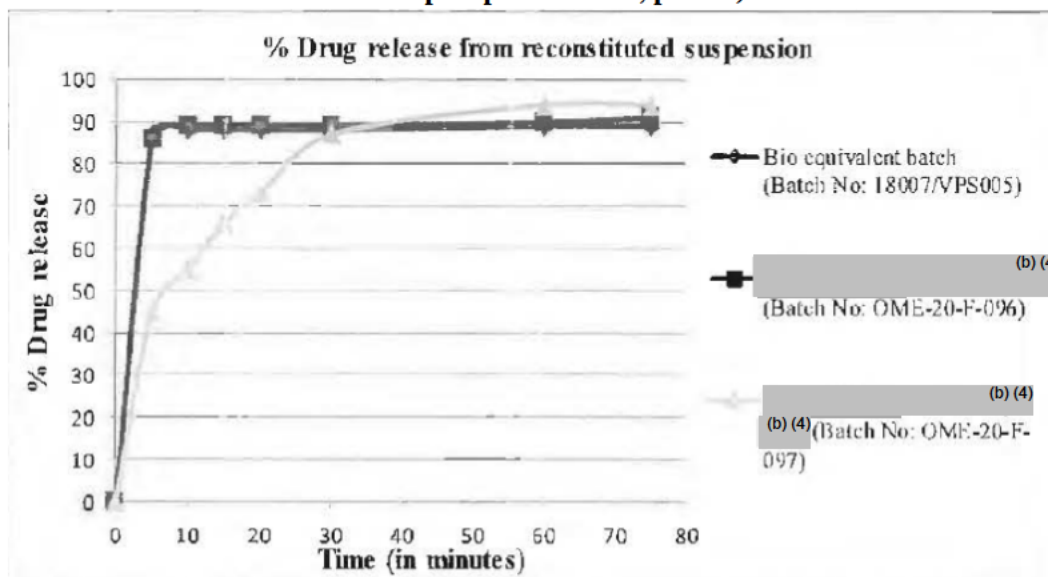
In the batch where (b) (4) was completely removed, dissolution significantly decreased, resulting in incomplete dissolution.

Figure 2. Impacts of (b) (4) amounts on dissolution of Omeprazole for Oral Suspension using the method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4)



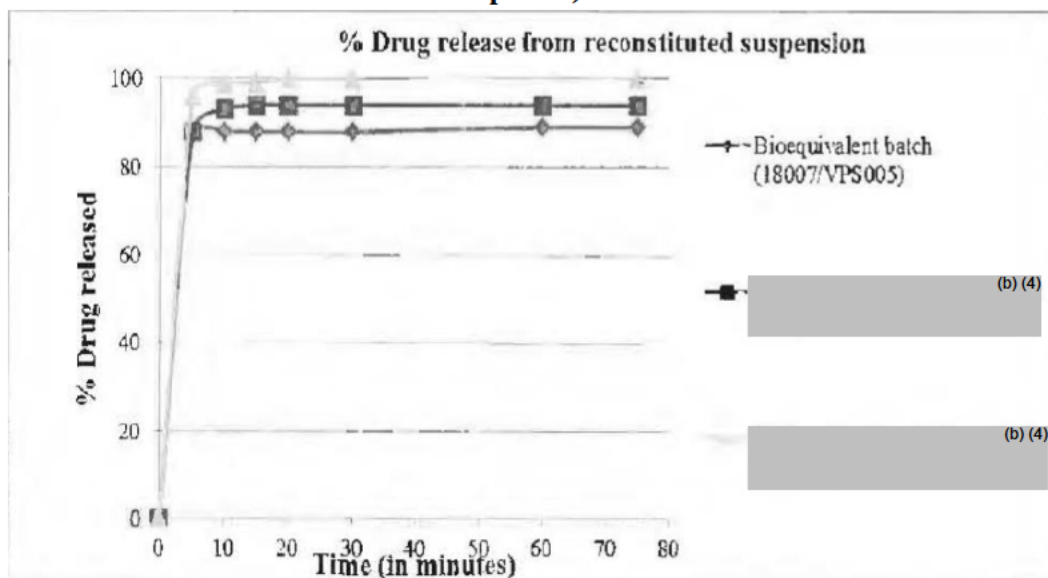
The dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4) was discriminating towards the changes in the amounts of (b) (4) with similarity factor, $f_2=30$ between the target batch vs. the batch manufactured with (b) (4) (Figure 3). For the batch manufactured with (b) (4) amount, dissolution significantly decreased at the early time points of 5–20 minutes.

Figure 3. Impacts of different (b) (4) amounts on dissolution of Omeprazole for Oral Suspension using the method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4)



The dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4) was not discriminating towards the changes in the amounts of (b) (4) (Figure 4).

Figure 4. Impacts of different (b) (4) amounts on dissolution of Omeprazole for Oral Suspension using the method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4)



Reviewer's Assessment on Dissolution Method:

The Applicant originally proposed a dissolution method (USP 2 at (b) (4) rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4). The originally proposed method was considered to be not

optimal

(b) (4)

The dissolution method with 25 rpm paddle speed (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4) was shown to be discriminating towards the changes in the amounts of (b) (4) and the changes in the amounts of (b) (4). Considering the achieved dissolution profile data and demonstrated discriminating ability, the dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4) is acceptable for the Quality Control of Omeprazole for Oral Suspension. An agreement on using the method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4) for the regulatory method for routine quality control testing of the proposed Omeprazole for Oral Suspension was reached between the Applicant and the Agency, dated 10/08/2020.

2.3 Dissolution data:

In the Response dated 06/11/2020, the Applicant provided dissolution data for Omeprazole for Oral Suspension 2 mg/mL clinical-batch and other registration batches (Table 3), using the originally proposed method (USP 2 at (b) (4) rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4). The dissolution at (b) (4)

(b) (4)

Table 3. Dissolution profiles for Omeprazole for Oral Suspension 2 mg/mL clinical batch 18007 and registration batches using the originally proposed dissolution method (USP 2 at (b) (4) rpm, in 900 mL

(b) (4)

In the Response dated 08/27/2020, the Applicant provided dissolution data for Omeprazole for Oral Suspension, using the method with (b) (4) paddle speed (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4), for the registration batches (Table 4). Using 25 rpm, there were (b) (4)% dissolution at 5 minutes and (b) (4)% at 15 minutes at a paddle speed of 25 rpm, for the proposed Omeprazole for Oral Suspension.

Table 4. Dissolution profiles (n=12) for Omeprazole for Oral Suspension registration batches sideways orientation under storage conditions ($5 \pm 3^{\circ}\text{C}$) for 24 months using the dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer solution, pH 7.4)

(b) (4)



2.4 Dissolution stability data:

In the Response dated 08/27/2020, the Applicant provided dissolution data for Omeprazole for Oral Suspension, using the method with lower paddle speed (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer, pH 7.4), for the clinical batch 18007 (Table 5).

Table 5. Dissolution profiles (n=12) for Omeprazole for Oral Suspension clinical batch 18007 under storage conditions (5 ± 3 °C) at 24 months using the dissolution method (USP 2 at 25 rpm, in 900 mL of 0.25 mM sodium phosphate buffer solution, pH 7.4)

(b) (4)

2.5 Dissolution acceptance criterion:

Based on the provided dissolution data, this Reviewer considers that the dissolution acceptance criterion “Q = $\frac{(b)}{(4)}$ % at 30 min” is acceptable.

3.

The Applicant conducted a relative bioavailability study of a single oral dose of Omeprazole for Oral Suspension kit (omeprazole/sodium bicarbonate, 40/1680 mg) vs. the Listed Drug (LD), Zegerid® (omeprazole/sodium bicarbonate) Powder for Oral Suspension, 40 mg/1680 mg, under fasted conditions in healthy subjects (Study OME-RM02-001).

(b) (4)

(b) (4)

(b) (4)

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MICROBIOLOGY

Product Information	(b) (4) 505(b)(2)
NDA Number	213593
Assessment Cycle Number	01
Drug Product Name / Strength	Omeprazole for Oral Suspension; Omeprazole USP/Sodium Bicarbonate USP 2 mg/mL omeprazole; 84 mg/mL NaHCO ₃
Route of Administration	Oral
Applicant Name	Azurity Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	CDER/OII/DG
Manufacturing Site(s)	<u>Omeprazole USP Powder & Omeprazole for Oral Suspension kit</u> CutisPharma, Inc. (Azurity Pharmaceuticals, Inc.) 841 Woburn Street, Wilmington MA 01887 <u>Strawberry-Flavored Diluent</u> (b) (4)
Method of Sterilization	Non-sterile

Assessment Recommendation: Adequate

Assessment Summary: The submission is **recommended** for approval.

List Submissions Being Assessed

Document(s)	eCTD	SDN	Date Received
NDA-213593-ORIG-1	0001	1	03/30/2020
NDA-213593-ORIG-1	0003	3	04/17/2020
NDA-213593-ORIG-1	0008	8	06/11/2020
NDA-213593-ORIG-1	0010	10	07/02/2020
NDA-213593-ORIG-1	0012	13	08/04/2020
NDA-213593-ORIG-1	0020	20	09/17/2020
NDA-213593-ORIG-1	0028	28	10/20/2020
NDA-213593-ORIG-1	0029	29	10/28/2020
NDA-213593-ORIG-1	0030	30	10/30/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: N/A

Concise Description of Outstanding Issues: The Division of Microbiology Assessment has no deficiencies or additional comments.

Supporting Documents: N/A

This NDA has 3 drug product modules. Each module is reviewed separately for ease of reference and comprehensibility.

- Omeprazole USP Powder (powder component of the kit)
- Strawberry-Flavored Diluent (liquid component of the kit)
- Omeprazole for Oral Suspension kit

Omeprazole USP Powder

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product

The subject drug product is a white to off-white powder packaged in a HDPE bottle (b) (4)) with an induction seal liner and a 38-400 mm (b) (4) cap.

Drug product composition

Ingredient	Amount per configuration			Conc. after constitution*	Function
	90 mL fill	150 mL fill	300 mL fill		
Omeprazole, USP	0.18 g	0.3 g	0.6 g	2 mg/mL	API

* with co-packaged Strawberry Flavored diluent

Description of container closure system

Configuration	Component	Description	DMF	Manufacturer
90 mL fill	Container	(b) (4) HDPE Bottles	(b) (4)	(b) (4)
150 mL fill		(b) (4)		
300 mL fill		(b) (4)		
90 mL fill	Closure	(b) (4) with a liner	(b) (4)	(b) (4)
150 mL fill		(b) (4)		
300 mL fill		(b) (4)		

Assessment: Adequate

The Applicant has provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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/s/

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