CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213593Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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

Date of This Memorandum:	August 18, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 213593
Product Name and Strength:	Konvomep (omeprazole and sodium bicarbonate for oral suspension), 2 mg/84 mg per mL
Applicant/Sponsor Name:	Azurity Pharmaceuticals, Inc.
OSE RCM #:	2020-675-3
DMEPA 1 Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on August 17, 2022 for Konvomep. Division of Gastroenterology (DG) requested that we review the revised label and labeling for Konvomep (Appendix A) to determine if it is acceptable from a medication error perspective.[a]

2 CONCLUSION

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

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

[a]Abraham, S. Label and Labeling Review for Konvomep (213593). Silver Spring (MD): FDA, CDER, OSE, DMEPA; 2022 AUG 10. RCM No.: 2020-675-2

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 10, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 213593
Product Name and Strength:	Konvomep (omeprazole and sodium bicarbonate for oral suspension), 2 mg/84 mg per mL
Applicant/Sponsor Name:	Azurity Pharmaceuticals, Inc.
OSE RCM #:	2020-675-2
DMEPA 1 Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 15, 2022 for Konvomep. Division of Gastroenterology (DG) requested that we review the revised label and labeling for Konvomep (Appendix A) to determine if it is acceptable from a medication error perspective.[a]

2 OVERRALL RISK ASSESSMENT

In review of the revised label and labeling received on July 15, 2022, DMEPA engaged in discussions with the Office of Pharmaceutical Quality (OPQ) and the Division of Gastroenterology (DG) regarding our previous recommendations surrounding the layout and presentation of the word "Diluent" and the active ingredients contained therewithin. It was concluded that the diluent bottle is not considered to be a finished drug product and therefore the diluent's active ingredient should not be formatted as an established name in the label and labeling. We have revised our previous recommendation as follows below in Table 1.

On July 12, 2022, an email from Azurity stated that, "(b) (4)

(b) (4)

[a]Abraham, S. Label and Labeling Review for Konvomep (213593). Silver Spring (MD): FDA, CDER, OSE, DMEPA; 2022 JUN 30. RCM No.: 2020-675-1

(b) (4)

We discussed (b) (4) with the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) and the Office of Compliance (OC). (b) (4) a linear barcode is required to be present on the label of a prescription drug per 21 CFR 201.25; under section 201(g)(1)(D) of the Federal Food Drug and Cosmetic Act, diluents are drugs if they are intended to be components of a drug.

3 CONCLUSION

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

Table 1. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Diluent Container Labels			
1.	In your July 12, 2022, email, you stated that, (b) (4)	We acknowledge your 15 July 2022 response to our Carton and Container Labeling Comments dated 08 Jul 2022 for Konvomep (NDA 213593). Your response indicated (b) (4)	(b) (4)

Table 1. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	(b) (4) (b) (4) (b) (4) (b) (4)	(b) (4) The linear barcode is required to be present on the label of a prescription drug as outlined in 21 CFR 201.25. Diluents are drugs under section 201(g)(1)(D) of the Federal Food Drug and Cosmetic Act if they are intended to be components of a drug. Please see the final Bar Code Label Requirement for Human Drug Products and Biological Products rule at 69 FR 9119 at 9129 for a discussion of the application of a linear barcode on a diluent label.	
2.	The Diluent is named as (b) (4)	We acknowledge that we requested you to revise the name presentation to include the established name, strength, and dosage form. However, the review team finds that the diluent bottle is not a finished drug product and therefore should not have a drug product established name. The previous presentation	Revise the diluent bottle name presentation similar to the label submitted on March 4, 2022 and note the additional suggested edits: **DILUENT** for **RECONSTITUTION** of Konvomep (omeprazole and sodium bicarbonate for oral suspension) **Contains:** sodium bicarbonate, USP, 84 mg/mL

Table 1. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		that highlights the diluent aspect along with including the name and amount of sodium bicarbonate on the label is more appropriate.	
3.	Important reconstitution statement lacks prominence.	Lack of prominence of important reconstitution information may result in Pharmacist overlooking important preparation information before dispensing to the patient. This may lead to preparation, administration errors and/or dosing errors.	Increase the prominence of reconstitution statement by highlighting the statement, increasing the font size and using the bolded font. For example, 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.
4.	Diluent container label is not adequately differentiated from the omeprazole container label.	Lack of adequate differentiation of diluent container label and omeprazole container may lead to preparation and dispensing errors.	Provide adequate differentiation between the diluent and omeprazole container labels. (b) (4) revise the diluent bottle label (b) (4) so that the diluent container label is primarily white.
5.	(b) (4)	(b) (4)	Remove the (b) (4) tatement from the diluent label.

Table 1. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4) [redacted]	
6.	The storage statement and the usual dose statement are bolded.	Overuse of bold font may diminish its effect on prominence for other important product information such as reconstitution statement.	Reserve the use of bolded font only for the most important product information on the label and labeling; remove the bold font from the storage statement and the usual dose statement.
Omeprazole Container Labels			
1.	The statement, "DISPENSE THIS BOTTLE TO THE PATIENT", lacks prominence.	Lack of prominence of this important information may result in diluent bottle being dispensed to the patient as the final drug product.	Increase the prominence, "DISPENSE THIS BOTTLE TO THE PATIENT", by increasing the font size.
2.	The usual dose statement is missing.	The usual dose statement is required as per 21 CFR 201.55.	Add a usual dose statement "Recommended Dosage: See prescribing information.
Konvomep Carton Labeling and Omeprazole Powder Container Labels:			
1.	The MG statement is bolded.	Overuse of bold font may diminish its effect on prominence for other important product information such as reconstitution statement.	Reserve the use of bolded font only for the most important product information on the label and labeling; remove the bold font from the MG statement.
2.	It is unclear if you are planning to have a paper copy of MG in the carton as it is not listed as one of the	Per 21 CFR 208.24(d), the MG needs to be enclosed in the carton for the pharmacist to dispense to patient.	Add MG to net contents on the carton labeling. Delete the sentence, (b) (4) [redacted] to avoid overcrowding of the PDP.

Table 1. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	items in the carton contents. It is unclear who the statement, (b) (4) is intended for.	The statement overcrowds the PDP and decreases the readability of more important reconstitution information.	

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/s/

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

PATIENT LABELING REVIEW

Date:	August 2, 2022
To:	Jay Fajiculay Regulatory Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	KONVOMEP (omeprazole and sodium bicarbonate for oral suspension)
Application Type/Number:	NDA 213593
Applicant:	Azurity Pharmaceuticals, Inc.

1 INTRODUCTION

On March 4, 2022, Azurity Pharmaceuticals, Inc. submitted for the Agency's review a Resubmission: Response to Complete Response (CR) Letter dated 28 January 2021, to the New Drug Application (NDA) 213593 for KONVOMEP (omeprazole and sodium bicarbonate for oral suspension). The purpose of this submission is to address deficiencies listed in the January 28, 2021 CR letter.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology (DG) on March 16, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for KONVOMEP (omeprazole and sodium bicarbonate for oral suspension).

2 MATERIAL REVIEWED

- Draft KONVOMEP (omeprazole and sodium bicarbonate for oral suspension) MG received on March 4, 2022, and received by DMPP and OPDP on July 25, 2022.
- Draft KONVOMEP (omeprazole and sodium bicarbonate for oral suspension) Prescribing Information (PI) received on March 4, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 25, 2022.
- ZEGERID (omeprazole and sodium bicarbonate) for oral suspension and capsules, for oral use comparator labeling dated March 4, 2022.

3 REVIEW METHODS

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

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

In our collaborative review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

Memorandum

Date: August 2, 2022

To: Jay R. Fajiculay, PharmD, Regulatory Project Manage (DG)

Joette Meyer, Associate Director for Labeling (DG)

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

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for Konvomep (omeprazole and sodium bicarbonate for oral suspension)

NDA: 213593

In response to DG's consult request dated March 16, 2022, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the original NDA submission for Konvomep.

Labeling: OPDP has no comments on the proposed labeling based on the draft labeling received by electronic mail from DG on July 25, 2022.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

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

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MEMORANDUM

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

Date of This Memorandum:	June 30, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 213593
Product Name and Strength:	Konvomep (omeprazole and sodium bicarbonate for oral suspension), 2 mg/84 mg per mL
Applicant/Sponsor Name:	Azurity Pharmaceuticals, Inc.
OSE RCM #:	2020-675-1
DMEPA 1 Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), medication guide (MG), container labels, and carton labeling received on March 4, 2022 for Konvomep. Division of Gastroenterology (DG) requested that we review the revised label and labeling for Konvomep (Appendix A) to determine if it is acceptable from a medication error perspective.

2 REGULATORY HISTORY

Azurity submitted a new NDA for Konvomep on April 15, 2020. We completed our label and labeling review on October 19, 2020, and provided our recommendation to DG and Azurity Pharmaceuticals Inc.[a] The application received a complete response (CR) letter on January 28, 2021, due to product quality and clinical issues. Azurity resubmitted their application on March 4, 2022.

In the resubmission, Azurity (b) (4) (b) (4) (b) (4) PI, MG, container labels, and carton labeling were revised to reflect the

[a]Abraham, S. Label and Labeling Review for Konvomep (213593). Silver Spring (MD): FDA, CDER, OSE, DMEPA; 2020 OCT 19. RCM No.: 2020-675

(b) (4) Additionally, Nasogastric and Orogastric administration instructions were added to Section 2.3 Preparation and Administration.

3 CONCLUSION

Our evaluation of the proposed Konvomep label and labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Table 1 for the DG and Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to Azurity Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

Table 1. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The diluent containing sodium bicarbonate is referred to as "Diluent" in Section 2.3 under steps for the preparation of suspension.	The diluent contains the active ingredient sodium bicarbonate. Therefore, naming it as "Diluent" is misleading. Additionally, container label will be labeled as sodium bicarbonate diluent.	Revise the term, "Diluent" to "sodium bicarbonate diluent" in section 2.3 steps for the preparation of suspension.
2.	The two sentences below the subheading '2.2 Dosage Regimen' lack readability.	Important dosage regimen information is presented under the heading of dosage regimen. Therefore, we recommend adding this important information as separate bullets for improved readability.	Consider bulleting the two statements immediately below Section 2.2 Dosage Regimen.
3.	As currently presented, the post reconstitution storage information is embedded in the steps for preparation of oral suspension.	Post reconstitution storage information will inform healthcare providers the post reconstitution storage information and minimize the risk of administering expired products.	Add post reconstitution information as a sub heading at the end of Section 2 and title as "Storage of Reconstituted Suspension".

Table 1. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	Step 14 in Section 2.3 under steps for the preparation of suspension states, "Instruct the patient to shake the reconstituted suspension well before each use and to use an oral dosing device that measures the appropriate volume (b) (4) (b) (4)	(b) (4)	Revise the statement to read, "Instruct the patient to shake the reconstituted suspension well before each use".
5.	The steps for preparation of suspension under Section 2.3 Preparation and Administration are lengthy and burdensome to read.	Typically, the Full Prescribing Information is intended for healthcare providers and not for patients. Konvomep is intended to be prepared by pharmacist before it is dispensed who are experienced with mixing oral suspension. Therefore, lengthy and burdensome directions are unnecessary.	Consider revising "Steps for Preparation of Suspension" to streamline the directions. For example, *Steps for the Preparation of Suspension* 1. Hold the neck of the bottle containing the omeprazole powder and tap all four of the bottom edges on a hard surface to loosen the powder before removing the cap. 2. Open the sodium bicarbonate diluent bottle and transfer about 1/3 of the contents of the Diluent bottle into the bottle containing omeprazole powder and shake the bottle vertically for approximately 30 seconds. 3. Add a second 1/3 of the sodium bicarbonate diluent into the omeprazole powder bottle and

Table 1. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			shake the bottle vigorously for approximately 30 seconds. 4. Add the remaining omeprazole bicarbonate diluent into the omeprazole powder bottle. Allow diluent to drain into the omeprazole powder bottle for 10 seconds and shake the omeprazole bottle vigorously for approximately 30 seconds. 5. Instruct the patient to shake the reconstituted suspension well before each use.
6.	Usage of confusing symbols or abbreviation (e.g.,"≥" "NG", "OG"s etc.)	The usage of symbols and abbreviations can cause misinterpretation and confusion.[b]	Replace the symbols and abbreviations with their intended meaning.
7.	As currently presented, the storage information of the reconstituted suspension is stated as step 13 under steps for the preparation of suspension.	Presenting important storage information to the reader in a text heavy format with decreased readability may lead to misinterpretation and improper storage of the product.	Relocate the storage information of reconstituted suspension to a new subheading in Section 2.3 under the title of "Storage of the Reconstituted Suspension".
Full Prescribing Information-Section 16 How Supplied/Storage and Handling			
1.	The following statements, "Protect from light", and "Protect from freezing" are found on the carton labeling, but they are absent in the PI.	Inconsistencies between PI and label and labeling may lead to misinterpretation in storage information.	Add the important storage statements, "Protect from light", and "Protect from freezing" to the PI.

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

Table 1. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
2.	The statements under storage subsection lack readability.	Lack of readability may lead to confusion of storage information for the healthcare providers.	Consider bulleting the statements under storage subsection.

Table 2. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
All Container Labels and Carton Labeling (Konvomep Carton labeling, Omeprazole Powder for Oral Suspension container labels, and Sodium Bicarbonate Diluent container labels)			
1.	A Medication Guide (MG) statement is not present on the PDP.	21 CFR 208.24(d).	Add a MG statement and ensure that it is prominently displayed.
Omeprazole Container Labels			
1.	The negative statement (b) (4) is found on the sodium bicarbonate diluent bottle.	Post-marketing reports have indicated that negative statements may have the opposite effect of the intended meaning because the word 'not' can be overlooked and the warning be misinterpreted as an affirmative action.[c]	Remove the negative statement from the diluent bottle and add an affirmative cautionary statement to container label. For example, **"DISPENSE THIS BOTTLE TO THE PATIENT"**
2.	As currently displayed, the storage statement competes for prominence with the cautionary reconstitution statement.	Lack of prominence of important reconstitution information may result in Pharmacist overlooking important preparation information before dispensing to the patient. This may lead to	Relocate the storage statement away from the cautionary reconstitution statement and remove bolded font from the statement.

[c] Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Safe Alert Acute Care. 2010;15(16):1-3.

Table 2. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		preparation, administration errors and/or dosing errors.	
3.	Important administration instruction, "Shake well before each use", is missing.	Once dispensed, it is possible that product may be stored in the container without a carton labeling. Therefore, it is important to have this administration instruction. Additionally, lack of prominence of important administration instruction may result in patient overlooking this information and lead to administration errors and/or dosing errors.	Add a bolded statement, "Shake well before each use" to the PDP.
Carton Labeling			
1.	As currently displayed, the manufacturer name("Azurity") is more prominent in size than the most important information (i.e., reconstitution statement, established name, strength, and dosage form)	The primary display panel (PDP) should be reserved for important product information. Duplicative manufacturer information located on the PDP takes readers' attention away from more important information such as reconstitution statement, established name, strength, and dosage form.	Remove the manufacturer name ("Azurity") from the PDP as it is already present on the back panel.

Table 2. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The flavor statement, "Strawberry Flavor" is found on the PDP.	PDP is reserved for the most important information. Other less important statements should be on the side panel.	Relocate the flavor statement, "Strawberry Flavor" to the back panel.
3.	Important reconstitution instructions to Pharmacist on the back panel lacks prominence.	Lack of prominence of important reconstitution instructions may result in Pharmacist overlooking important preparation information before dispensing to the patient. This may lead to preparation, administration errors and/or dosing errors.	Increase the prominence of important reconstitution instructions on the back panel by increasing the font size.
4.	The route of administration sentence on the side panel, (b) (4) is redundant.	Dosage form (oral suspension) on the PDP indicates the route of administration is oral.	Remove the sentence, (b) (4)
5.	The storage information presented on the side panel lacks prominence.	We recommend to revise the storage information to an affirmative statement for result in the desired action of storage.	Revise the statement to read "Kit must be refrigerated at 2°to 8°C (36° to 46°F)."
6.	Important administration instruction found on the back panel, "Shake well before each use" lacks prominence.	Lack of prominence of important administration instruction may result in patient overlooking important administration information leading to administration errors and/or dosing errors.	Bold the statement, "Shake well before each use" and relocate to the PDP.

Table 2. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
7.	Carton labeling is missing the reconstitution expiration date statement, "Discard after Month/Day/Year".	Allowing space for healthcare providers to write post-reconstitution expiration date on the label will inform persons responsible for preparing the product and minimize the risk of administering expired products. "Discard after __/__/__" is an affirmative statement, and has been shown to result in the desired action. Additionally, the "__/__/__" statement will alert the healthcare provider to write a complete date (month, day, and year) on the container labels and carton labeling.	We recommend adding the reconstitution expiration statement, "Discard after __/__/__" on the carton labeling.
Konvomep Carton Labeling and Omeprazole Powder Container Labels:			
1.	The strength statement lacks prominence.	21 CFR 201.15(a)(6)	We recommend that you increase the prominence of the strength statement by increasing the font size on the container labels. Relocate the strength statement to directly below the established name in a centered position.
2.	Important reconstitution statement on PDP lacks prominence.	Lack of prominence of important reconstitution information may result in Pharmacist overlooking important preparation information before	Add the bolded statement, "NOTE TO PHARMACIST" and increase the prominence of reconstitution statement by increasing the font size. For example,

Table 2. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		dispensing to the patient. This may lead to preparation, administration errors and/or dosing errors.	IMPORTANT NOTE TO PHARMACIST: Must Reconstitute before dispensing
Omeprazole Container Labels and Diluent Labels			
1.	As currently displayed, the manufacturer name("Azurity") is more prominent in size than the most important information (i.e., established names, strength, and dosage form).	This takes readers' attention away from other important information such as established name(s), strength, dosage form, and cautionary reconstitution statements.	Decrease prominence of the manufacturer name on the PDP.
Diluent (Sodium Bicarbonate) Container Labels			
1.	The primary product (sodium bicarbonate) that is contained within the bottle (i.e. name and strength) is lacking prominence. Additionally, the dosage form is missing on the label.	Lack of prominence of the active ingredient name, strength, and dosage form in the diluent may lead to confusion for the pharmacist mixing the product leading to drug preparation errors.	Revise the name presentation to include the established name, strength, and dosage form. For Example, SODIUM BICARBONATE oral solution, USP 84 mg/mL DILUENT For KONVOMEP for oral suspension Delete the less prominent statement of established name and the strength presentation, "Contains the sodium

Table 2. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			bicarbonate, USP 84 mg/mL" to make room for more important information.
3.	The cautionary statement, "**Important**...." lacks prominence and it is not clear to whom the statement is addressed to.	Lack of prominence of important reconstitution information may result in Pharmacist overlooking important preparation information before dispensing to the patient. This may lead to preparation, administration errors and/or dosing errors.	Revise the statement to add the bolded words, "**IMPORTANT NOTE TO PHARMACIST:** Add contents...." and increase the prominence of rest of the reconstitution statement by increasing the font size.
4.	The usual dose statement is missing.	The usual dose statement is required as per 21 CFR 201.55.	Add a usual dose statement "Recommended Dosage: See prescribing information.
5.	The statement, (b) (4) is found on the label.	This statement is unnecessary as it is understood that (b) (4) are in the full prescribing information. Additionally, it provides no added benefit to the reader.	Delete the statement, (b) (4) ."to make room for more important information.
6.	The lot number statement is missing.	The lot number statement is required as per 21 CFR 201.10(i)(1).	Display the intended placement of the lot number statement.
7.	The expiration date missing.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Display the intended placement of the expiration date and identify the format as recommended below. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if

Table 2. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
8.	The National Drug Code (NDC) number is missing from diluent container labels.	Per 21 CFR 207.33 and 21 CFR 201.2, drug products subject to listing with the FDA is requested to have a unique NDC number to identify its labeler, product, and package size and type.	We encourage you to add the NDC number to the diluent bottles ensuring different NDC package codes (last two digits of the NDC number) are used for different net quantities of the diluent.
9.	The linear barcode is missing from diluent container labels.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature.	Add a linear barcode to diluent container labels.

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

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

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

Date of This Review:	October 19, 2020
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 213593
Product Name and Strength:	Konvomep (omeprazole and sodium bicarbonate) for oral suspension, 2 mg/84 mg per mL
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Azurity Pharmaceuticals, Inc.
FDA Received Date:	April 15, 2020 and May 15, 2020
OSE RCM #:	2020-675
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Konvomep (omeprazole and sodium bicarbonate) for oral suspension, the Division of Gastroenterology (DG) requested that we review the proposed Konvomep prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Appropriate description of product characteristics that are important to facilitate identification of the product dosage form are missing from Section 3 Dosage forms and	Per CFR 201.57(c)(4)(ii), this information is necessary to facilitate identification of the dosage form.	Include information about color and other identifying characteristics to help facilitate product identifications and mitigate the potential use of adulterated product.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	Strengths and Section 16 How Supplied/Storage and Handling.		
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Recommended dosage in Table 1 titled "Recommended Dosage Regimen of Konvomep (b) (4), 2 mg/mL by Indication for Adults (b) (4) have doses (b) (4)	Presentation of dosage in (b) (4) might create confusion resulting in underdose or overdose error (b) (4)	We recommend having the recommended dosage in (b) (4) mg (b) (4) aligning the content and format of Table 1 to the Dosage Regimen table located in the Dosage and Administration section of the highlights.
2.	(b) (4)		
3.	Duplicative information is provided in the beginning of section 2.3 Preparation and Administration about the contents of the kit.	The contents of the kit is already listed in Section 16 How Supplied/Storage and Handling.	We recommend deleting the sentences regarding the contents of the kit and retaining the sentence about a healthcare provider (i.e., pharmacist) must reconstitute the solution.
4.	Steps for preparation of suspension under Section 2.3 Preparation and Administration are lengthy and burdensome to read.	Typically, the Full Prescribing Information is intended for healthcare providers and not for patients. Konvomep is intended to be prepared by pharmacist before it is dispensed.	We recommend the applicant to revise (b) (4) " to streamline the directions.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The National Drug Code (NDC) numbers for carton labeling and	Per 21 CFR 207.33 and 21 CFR 201.2, drug products subject to listing with the FDA is requested to have a	Add the NDC number for each of the carton labeling and diluent container labels to the

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	diluent container labels are missing from the PI.	unique NDC number to identify its labeler, product, and package size and type.	How Supplied/Storage and Handling section.
2.	The statement, (b) (4) [redacted] is found in Section 16 How Supplied/Storage Information and Handling.	The Prescribing Information is intended for healthcare providers and not for patients.	We recommend deleting the statement, (b) (4) [redacted]

Table 3. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
All Container Labels and Carton Labeling (Kovnomep Carton labeling, Omeprazole Powder for Oral Suspension container labels, and Diluent (sodium bicarbonate) container labels)			
1.	The dosage form statement has more prominence than other more important product information such as the strength.	As currently displayed, the dosage form statement has more prominence than the strength statement.	Unbold the dosage form statement.
2.	The "Rx only statement" is overtly prominent.	The increased prominence of the "Rx only statement" takes the reader's attention away from other important information on the PDP such as established name, dosage form, and strength statement.	Decrease the prominence of the "Rx only statement" by decreasing the font size and unbolding the font.

Table 3. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The "Usual Dose" statement is missing.	The "Ususal Dose" statement is required as per 21 CFR 201.55.	Include a usual dose statement to the side panel, "Recommended Dosage: See prescribing information."
4.	The format for expiration date is incorrect.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Submit expiration date in the format that is stated below. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Omeprazole Powder for Oral Suspension Container Labels			
5.	The strength statement is missing from the 300 mL container label.	21 CFR 201.15(a)(6)	Add the strength statement taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Consider relocating to a more prominent position on the Principal Display Panel (PDP).
6.	Omeprazole powder for oral suspension container labels are missing the reconstitution expiration	Allowing space for healthcare providers to write post-reconstitution expiration date on the label will inform persons	We recommend adding the reconstitution expiration statement, "Discard after __/__/__" on omeprazole powder for oral suspension container labels.

Table 3. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	date statement, "Discard after Month/Day/Year".	responsible for preparing the product and minimize the risk of administering expired products. "Discard after __/__/__" is an affirmative statement, and has been shown to result in the desired action. Additionally, the "__/__/__" statement will alert the healthcare provider to write a complete date (month, day, and year) on the container labels and carton labeling.	
7.	Important reconstitution statements to the Pharmacist lack prominence.	Lack of prominence of important reconstitution information may result in Pharmacist overlooking important preparation information before dispensing to the patient. This may lead to preparation, administration errors and/or dosing errors.	Relocate, bold and consider boxing the reconstitution statement on the PDP. For example, Reconstitute before dispensing Once reconstituted, dispense this bottle to the Patient.
Konvomep Carton Labeling			
1.	Important reconstitution statement is located on the side panel.	Lack of prominence of important reconstitution information may result in Pharmacist overlooking important preparation information before dispensing to the patient. This may lead to preparation,	Relocate, bold and consider boxing the reconstitution statement to the PDP. For example, Reconstitute before dispensing

Table 3. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		administration errors and/or dosing errors.	
2.	The storage statement "Must be refrigerated" is on the PDP.	PDP is reserved for the most important information. The storage information should be on the side panel.	Remove the storage statement from the PDP.
3.	As currently displayed, the statement, "EACH KIT INCLUDES" is bolded. Additionally, important information such as Tradename and strength are missing from the statement, "one bottle containing XX mg of omeprazole powder". The second bottle containing sodium bicarbonate is referred to as "Strawberry flavored diluent" when the active ingredient is sodium bicaronate.	The primary display panel (PDP) should be reserved for important product information. Unimportant bolded statement (EACH KIT INCLUDES) on the PDP takes readers' attention away from more important information such as proprietary and established names, strength, and dosage form. Absence of clear labeling with important information may lead to confusion and cause dosing errors.	Unbold the sentence, *EACH KIT INCLUDES*, and revise the list to include the drug name and strength of each product listed, for example: Each kit includes: 1 bottle of DRUGNAME (established name) dosage form, strength 1 bottle of sodium bicarbonate diluent for DRUGNAME, XX mL 1 prescribing information (b) (4)
4.	It is unclear where the machine-readable product identifier is located on the label.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. Include the machine-readable data matrix barcode to the carton labeling. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number]

Table 3. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			EXP: [insert expiration date] We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.
Konvomep Carton Labeling and Omeprazole Powder for Oral Suspension Container Labels:			
1.	As currently displayed, the strength statements on the 90 mL and 150 mL container labels and carton labeling lack prominence.	21 CFR 201.15(a)(6)	We recommend that you increase the prominence of the strength statement taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Consider relocating to a more prominent position on the Principal Display Panel (PDP).
2.	The strength statement of omeprazole is presented in 'mg' (2 mg) and the net quantity statement of omeprazole powder ('this bottle contains 0.XX g of omeprazole powder) is expressed in 'g' (grams).	Presentation of omeprazole powder in two different units might create confusion resulting in underdose or overdose errors.	We recommend aligning the net quantity statement ('this bottle contains 0.XX g of omeprazole powder') to 'mg' to be consistent with the strength statement.
3.	The storage information includes the use of error prone symbols, such as "-" and/or "/".	Lack of clarity. Misinterpretation and confusion over symbols may lead to prescribing or administration errors.	Revise the storage statement sentences without symbols and to be consistent with the prescribing information.
Diluent (Sodium Bicarbonate) Container Labels			

Table 3. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	As currently displayed, the "TRADENAME" presentation has more prominence than the word "DILUENT".	Increased prominence of the Tradename presentation on the diluent label may cause confusion between the diluent bottle and the powder for oral suspension bottle.	Revise the presentation of diluent and Tradename ensuring the word diluent is most prominently displayed on the PDP: For example, **Diluent** For DRUGNAME for oral suspension
5.	The National Drug Code (NDC) number is missing from diluent container labels.	Per 21 CFR 207.33 and 21 CFR 201.2, drug products subject to listing with the FDA is requested to have a unique NDC number to identify its labeler, product, and package size and type.	Add the NDC number to the diluent bottles ensuring different NDC package codes (last two digits of the NDC number) are used for different net quantities of the diluent.
6.	The linear barcode is missing from diluent container labels.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature.	Add a linear barcode to diluent container labels.
7.	The storage statement is missing from the diluent container labels.	The storage information is needed for the correct storage and handling of the diluent.	Add the storage statement to the diluent container labels.

4 CONCLUSION

Our evaluation of the proposed Konvomep prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Azurity Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Konvomep that Azurity Pharmaceuticals, Inc. submitted on May 15, 2020.

<table>
<tr><th colspan="2">Table 4. Relevant Product Information for Konvomep</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>omeprazole and sodium bicarbonate</td></tr>
<tr><td>Indication</td><td>Indicated in adults for
(b) (4)
• Treatment of active benign gastric ulcer
(b) (4)
• Reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>for oral suspension</td></tr>
<tr><td>Strength</td><td>2 mg/84 mg
The reconstituted product contains 2 mg/mL of omeprazole and 84 mg/mL of sodium bicarbonate.</td></tr>
<tr><td>Dose and Frequency</td><td><table><tr><th>Indication</th><th>Recommended Adult Dosage</th></tr><tr><td colspan="2">(b) (4)</td></tr><tr><td>Active Benign Gastric Ulcer</td><td>40 mg once daily for 4 to 8 weeks</td></tr><tr><td colspan="2">(b) (4)</td></tr><tr><td>Reduction of Risk of Upper GI Bleeding in Critically Ill Patients</td><td>40 mg initially followed by 40 mg 6 to 8 hours later and 40 mg once daily thereafter for 14 days</td></tr></table></td></tr>
<tr><td>How Supplied</td><td>Each Konvomep kit contains one bottle of omeprazole USP, a white to off-white powder for oral suspension, and one bottle of pre measured Strawberry Flavored Diluent containing sodium</td></tr>
</table>

	bicarbonate, in the strengths and volumes listed in 90 mL, 150 mL, and 300 mL. [redacted] (b) (4).
Storage	Store Konvomep kit in the refrigerator, 2° to 8°C (36° to 46°F). Store reconstituted suspension of Konvomep in the refrigerator, 2° to 8°C (36° to 46°F). Keep containers tightly closed. Discard Konvomep Oral Suspension after 30 days
Reference Listed Drug (RLD):	Zegerid (omeprazole/sodium bicarbonate) Powder for Oral Suspension (NDA 021636) Prilosec (omeprazole) Delayed-Release Pellets (NDA 019810).

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Konvomep labels and labeling submitted by Azurity Pharmaceuticals, Inc.

- Container label(s) received on April 15, 2020
- Carton labeling received on April 15, 2020
- Prescribing Information (Image not shown) received on May 15, 2020 \\CDSESUB1\evsprod\nda213593\0005\m1\us\114-labeling\draft\annotated\annotated-us-prescribing-information-uspi-pdf.pdf

F.2 Label and Labeling Images

Omeprazole Powder for Oral Suspension Container Labels and Sodium Bicarbonate Diluent Container Labels:

(b) (4)

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Date: October 16, 2020 **Date consulted:** 4/10/2020

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

To: Division of Gastroenterology (DG)

Drug: Omeprazole/sodium bicarbonate for Oral Suspension

NDA: 213593

Applicant: Azurity Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Formatting Recommendations

Indication:

(b) (4)

- Short-term treatment (4 to 8 weeks) of active benign gastric ulcer.

(b) (4)

- Reduction of risk of upper GI bleeding in critically ill adult patients.

Materials Reviewed:

- March 30, 2020, Initial submission for NDA 213593 including labeling in PLLR
- April 10, 2020, DG consult, DARRTS Reference ID 4590186
- May 15, 2020, the applicant's response to the April 23, 2020 information request (IR) by the Agency.
- May 15, 2020, revised labeling in PLLR.

- February 1, 2019, Labeling review for Zegerid (oral suspension and capsules-omeprazole and sodium bicarbonate), NDA 021636/S-020 by Christos Mastroyannis, M.D., in DARRTS, Reference ID: 4377778[1]
- November 23, 2016, Prilosec (omeprazole) and Nexium (esomeprazole magnesium) labeling reviews NDA 22056/S-019 and 21957/S-018 respectively, by Christos Mastroyannis M.D., in DARRTS, Reference ID: 4017935[1]
- January 15, 2016, Labeling review for Prilosec (omeprazole magnesium) Delayed-Release Oral Suspension NDA 022056/S-018 by Christos Mastroyannis, M.D., in DARRTS, Reference ID: 3873309[1].

Consult Question: Review of the FPI for PLLR compliance, and any additional labeling recommendations from the Maternal Health Team to ensure the safe use of Omeprazole for Oral Suspension kit in patients of childbearing potential.

INTRODUCTION

On March 30, 2020, the applicant, Azurity Pharmaceuticals, Inc., submitted an original application for Omeprazole for Oral Suspension kit under the 505(b)(2) pathway. The Division of Gastroenterology (DG) consulted the Division of Pediatric and Maternal Health (DPMH) on April 10, 2020, to assist with Pregnancy and Lactation Labeling Rule (PLLR) requirements for the *Pregnancy* and *Lactation* subsections of labeling.

BACKGROUND

Regulatory History

Azurity Pharmaceuticals, Inc. submitted an original application for Omeprazole for Oral Suspension kit under the 505(b)(2) pathway, that is indicated in adults for:

(b) (4)

- Short-term treatment (4 to 8 weeks) of active benign gastric ulcer.

(b) (4)

- Reduction of risk of upper GI bleeding in critically ill adult patients.

The drugs relied upon are Zegerid Powder for Oral Suspension, NDA 021636 and Prilosec Capsules, NDA 019810.

[1] The November 23, 2016 Prilosec (omeprazole) and Nexium (esomeprazole magnesium) labeling reviews NDA 22056/S-019 and 21957/S-018, and January 15, 2016 Labeling review for Prilosec (omeprazole magnesium) Delayed-Release Oral Suspension NDA 022056/S-018 by Christos Mastroyannis, M.D, respectively, were part of the materials reviewed for the background section but were not a source relied upon for the labeling recommendations for this consult.

Drug Characteristics[2]

Table 1: Drug Characteristics

Drug Class	Proton Pump Inhibitor (PPI) and Sodium Bicarbonate Buffer
Mechanism of Action	Omeprazole is an antisecretory compound containing benzimidazoles, that suppresses gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. The gastric acid-pump inhibitor blocks the final step of acid production. This effect is dose related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. The sodium bicarbonate in the diluent acts to protect omeprazole from degradation due to the gastric acid.
Molecular Weight	345.42 Daltons
Protein Binding omeprazole	95% bound to plasma proteins
Mean plasma Half-Life	omeprazole: approximately 1 hour (0.4 to (b) (4) hours); half-life for sodium bicarbonate is unknown
Bioavailability omeprazole	Absolute bioavailability of about (b) (4) % following oral dose of (b) (4) 40 mg administration
HCO_3^-	Bicarbonate is a normal constituent of body fluids and plasma concentration is regulated by the kidney. Treatment with exogenous sodium bicarbonate increases plasma bicarbonate, buffers excess hydrogen ion concentration, and raises blood pH Sodium bicarbonate's primary role is to neutralize gastric acid and protect omeprazole from gastric acid degradation, until it can be absorbed. Sodium bicarbonate is not an active ingredient in the TRADENAME.
Formulation	The reconstituted Omeprazole for Oral Suspension kit suspension contains 2 mg/mL omeprazole and 84 mg/mL of sodium bicarbonate (equivalent to 1 mEq/mL of sodium).

REVIEW

PREGNANCY

Nonclinical Experience

The applicant did not perform any nonclinical studies and relies upon Zegerid Powder for Oral Suspension, NDA 021636 and Prilosec Capsules, NDA 019810. The applicant did not provide any new nonclinical studies that have been identified in the scientific literature. As per the Zegerid labeling of September 24, 2019,

> Omeprazole
> Reproduction studies in rats and rabbits resulted in dose-dependent embryo-lethality at omeprazole doses that were approximately 3.4 to 34 times an oral human dose of 40 mg (based on a body surface area for a 60 kg person). Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole (an enantiomer of omeprazole) magnesium in

[2] Applicant's Omeprazole for Oral Suspension kit proposed Labeling of March 30, 2020 and Zegerid (oral suspension and capsules-omeprazole and sodium bicarbonate) existing labeling of September 24, 2019

rats and rabbits during organogenesis with doses about 68 times and 42 times, respectively, an oral human dose of 40 mg esomeprazole or 40 mg omeprazole (based on body surface area for a 60 kg person). Changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age.

Sodium Bicarbonate
Published animal studies report that sodium bicarbonate administered to rats, mice or rabbits during pregnancy did not cause adverse developmental effects in offspring.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature on the effects of omeprazole and/or sodium bicarbonate exposure during pregnancy, lactation, and on females and males of reproductive potential using the following search terms:

"omeprazole" [MeSH] AND/OR "sodium bicarbonate" [MeSH] OR "proton pump inhibitor" [tiab] OR "pregnancy" [MeSH] OR "pregnan*" [tiab] "adverse pregnancy outcome" [MeSH] OR "fetal abnormality" [MeSH] OR "congenital malformations" [MeSH] OR "teratogenic effects" [MeSH].

The reader is referred to the applicant's submission "Response to IR" of May 15, 2020, for the complete search criteria. This search revealed 284 publications, of which 266 were removed for one or more of the following reasons:

- General irrelevancy
- Duplication (same article was provided under different keyword results)
- No substantive data or information related to pregnancy, lactation or reproduction
- Non-relevant indication
- Discussed omeprazole and/or sodium bicarbonate only when administered as collateral medications with other therapies and not as a primary intervention

Overall, the literature search provided a total of 12 publications related to pregnancy, and one publication for pregnancy and lactation.

Prolonged experience from the published literature with omeprazole use during pregnancy, has not identified a drug-associated risk of major congenital anomalies, or miscarriage or other adverse pregnancy outcomes with first trimester omeprazole use. A review of the published literature for relevant data regarding sodium bicarbonate used in pregnant women revealed no new safety concerns. See Appendix 1 for the referenced publications.

***Table 2: Specific Congenital Malformations Seen After First Trimester Exposure to Omeprazole**

Congenital malformation	# (N)	Other drugs used
Relatively major malformations		
Ventricular septal defect	3	None, None, and Ergotamine + diazepam + propranolol
Persistent ductus arteriosus at term (37 and 38 weeks)	2	None, None
Unspecified cardiac defect	2	None, Norfloxacin + ranitidine + sucralfate
Hydronephrosis	2	None, Citalopram + carisoprodol + cetirizine + oral contraceptive
Hypospadias	1	Ranitidine
Urethral stenosis	1	Iron and vitamins
Bladder exstrophy	1	None
Plagiocephaly	1	Ranitidine
Facial anomaly	1	Meclozine
Down's syndrome (mother 34 years)	1	None
Tetralogy of Fallot+eye malformation (coloboma +posterior segment malformation)	1	None
Malformations only identified in the hospital discharge register		
Ventricular septum defect	2	None, Salbutamol
Pylorostenosis	2	Antacids, Sucralfate

Reviewer Comment
It is not known why the applicant did not identify any publications with Na^+ bicarbonate use during pregnancy. The reader is referred to the DPMH literature review below.

DPMH's Review of Literature
In addition to the search of published literature performed by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for omeprazole and sodium bicarbonate and use in pregnancy. No additional published safety information was identified. The reader is referred to the reviews of NDA 021636/S-020, NDA 22056/S-019 and NDA 022056/S-018 by Christos Mastroyannis, M.D.[1]

Sodium Bicarbonate
GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation report that "No reports of human 1st trimester use of sodium bicarbonate in pregnancy have been located.

There is a report in the literature of one woman who developed hypokalemia,

rhabdomyolysis, and cardiomyopathy in late gestation who was found to have a history of baking soda (pica) during pregnancy. The conditions were reversed with the cessation of the pica.[3] One teaspoon of baking soda (pica) contains 4.8 gm (59 mEq) of sodium bicarbonate, which amount is much higher than what is included in Omeprazole/sodium bicarbonate for Oral Suspension. From the limited data, it appears that sodium bicarbonate did not have any teratogenic effects when administered during pregnancy in animals. Up to 20 mEq of sodium bicarbonate daily may not disturb the electrolyte balance. The amount of sodium bicarbonate can easily be handled by the kidney as the sodium load, but it should be used in caution in patients who have underlying renal disease, fluid retention/edema, or acid-base disturbances. Pregnant women in general do not fall in these categories and they may handle the excess Na^+ and bicarbonate as normal individuals do.

Omeprazole

In the study by Zhang Y, et. al, 2019, a retrospective cohort study, the authors analyzed ~ 9.5 million FDA adverse effect reports to identify drugs with increasing risks of cholestasis as an adverse effect. The cholestasis cohort contained 17,385 records and the non-cholestasis cohort contained 9,408,128 records. The odds ratio analysis reveals that omeprazole use is associated with an increased risk of cholestasis by a factor of 2.61 [2.54, 2.69] vs subjects who did not take omeprazole. In addition, pregnant women inherently carry an increased risk of cholestasis. Therefore, pregnant women on omeprazole have a higher risk of cholestasis vs non pregnant women. The cholestasis risk has not been systematically studied, other than some case reports.[4,5,6.] These findings provide some evidence of potential risks of cholestasis with omeprazole. Limitations of this study include that data in FAERS/AERS may over-represent patients with adverse effects and overlook patients who did not experience adverse effects when using a drug. Cholestasis occurs during pregnancy in absence of omeprazole. More studies are needed to further elucidate this adverse reaction in order to be considered to be included in the labeling.

An Office of Surveillance and Epidemiology (OSE) review dated January 15, 2014, assessed ten published observational studies of PPIs to determine if there is sufficient evidence to justify the sponsor's changes to the labeling in regard to the risk of PPIs use in pregnancy and congenital malformations. OSE concluded that the results showed a statistically insignificant risk (see reviews in DARRTS by Jeanine Best of 11/15/2013 and Robert Campbell of 1/15/2014). Further review of Cochrane Pregnancy and Childbirth Group's Trials Register (June 30, 2015), ClinicalTrials.gov (March 2, 2015), as well as PubMed search for terms as Prilosec or omeprazole or PPI and pregnancy or lactation, as of 2013 to 2015, did not produce any helpful additional publications.

Reviewer Comment

The association of proton pump inhibitors (PPIs) and asthma suggested in published literature is not further discuss here. It has previously been evaluated by the Division, DEPI and DPARP [currently Division of Pulmonology, Allergy and Critical Care (DPACC)]. The Division concluded that there was not sufficient information to support asthma as an adverse reaction for

[3] Grotegut CA, Dandolu V, Katari S, Whiteman VE, Geifman-Holtzman O, Teitelman M. Baking soda pica: a case of hypokalemic metabolic alkalosis and rhabdomyolysis in pregnancy. Obstet Gynecol 2006;107:484-6.

[4] Sanchez Garrido A. Omeprazole-induced acute cholestatic hepatitis. Gastroenterol Hepatol 2007,30:54.

[5] Namba S. Inhibitory effects of omeprazole and cimetidine on the formation of gastric ulcer in rats with obstructive jaundice and acute renal failure. Nihon Shokakibyo Gakkai Zasshi 1988,85:1223–1232.

[6] Riedmaier S, Klein K, Winter S, Hofmann U, Schwab M, Zanger U. Paraoxonase (PON1 and PON3) Polymorphisms: Impact on Liver Expression and Atorvastatin-Lactone Hydrolysis.Frontiers in Pharmacology 2011,2:415

drug class labeling of PPIs. This decision was based on DEPI's review of the data that concluded

> *The weight of evidence available from the observational studies showed a higher frequency of allergy, including asthma, in children with prenatal exposure to PPI or H2RA. Bias due to confounding plausibly explains this association. The literature reviewed by DEPI contained very limited evidence for causal association between prenatal exposure to PPI or H2RA and childhood allergy. DEPI recommended that DGIEP consider the weak evidence for causality before deciding to add information from epidemiologic studies about prenatal PPI and childhood asthma or allergic disease to the FDA label.*[7,8,9]

While DPARP "acknowledges the occurrence of Type I-like hypersensitivity reactions with PPIs and the possibility of an increase in atopic diseases such as food allergy and asthma with gastric acid suppression therapy, concludes that the DPV data mining results and the literature reports do not support changing the current prescription or drug facts labeling for hypersensitivity reactions to PPIs."[10]

Rebecca Devine et. al.[11] *in a letter to the editor of Journal of Allergy and Clinical Immunology in reference to "Acid-suppressive medications during pregnancy and risk of asthma and allergy in children: A systematic review and meta-analysis" states: "Our findings of increased risk may reflect a true risk or may be explained by residual confounding and/or confounding by indication. Of note is that none of the studies adjusted for the full panel of known confounders in these associations".*

Review of Pharmacovigilance Database (PV)

The applicant did not provide a PV review because the drug is marketed neither in the US nor outside of the U.S.; therefore, a PV database has not yet been established.

Pregnancy Registry

There is no pregnancy registry.

Utilization

No utilization information exists because the drug has not yet been marketed.

Summary

No major birth defects or miscarriage have been identified with use of the combination product or its components in pregnancy. There is no evidence of embryofetal toxicity in animal reproduction studies performed with sodium bicarbonate. No studies exist of sodium bicarbonate use in pregnancy.

As stated in a previous DPMH review of "Prilosec and Pregnancy"[12] for the Pregnancy and Nursing Mothers Labeling, an expert review of published data on experiences with omeprazole use during

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[7] Weissfeld, JL, K Leishear-White, and L Taylor, Gastric Acid Suppression during Pregnancy and Risk of Childhood Allergy, filed under Protonix® NDA 209463 on March 6, 2017 (Reference ID: 4064920).

[8] cLeishear, K, SK Sandhu, and D Shih, Literature Review of the Safety of H2-receptor Antagonist Use during Pregnancy, filed under Pepcid® AC NDA 019462 on December 12, 2104 (Reference ID: 3671765).

[9] Weissfeld, JL, K Leishear-White, and L Taylor, Gastric Acid Suppression during Pregnancy and Risk of Childhood Allergy, filed under Protonix® NDA 209463 on March 6, 2017 (Reference ID: 4064920).

[10] Paterniti B, MD Medical Officer DPARP Proton Pump Inhibitors and Gastric Acid Suppression Hypersensitivity, April 27, 2016

[11] Weissfeld, JL, K Leishear-White, and L Taylor, Gastric Acid Suppression during Pregnancy and Risk of Childhood Allergy, filed under Protonix® NDA 209463 on March 6, 2017 (Reference ID: 4064920).

[12] •January 15, 2016, Labeling review for Prilosec (omeprazole magnesium) Delayed-Release Oral Suspension NDA 022056/S-018 by Christos Mastroyannis, M.D., in DARRTS, Reference ID: 38733091

pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair). No new data on safety concerns related to omeprazole use during pregnancy has been published since this last review.

LACTATION

Nonclinical Experience

The Pharmacology/Toxicology data have been previously reviewed and remain unchanged. There are no nonclinical findings on the effects of omeprazole or sodium bicarbonate on lactation in animals.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature on the effects of omeprazole and/or sodium bicarbonate exposure during lactation, using the following search terms: "omeprazole" [MeSH] AND/OR "sodium bicarbonate" [MeSH] OR "proton pump inhibitor" [tiab] OR "lactation" [MeSH] OR "breastfeeding" [tiab].

The reader is referred to the applicant's submission "Response to IR" of May 15, 2020, for the complete search criteria. This search revealed 4 publications related to omeprazole (see Table 3 below). Two publications, one by Thélin CS, *et.al.*[30] and one by Nava-Ocampo AA, *et. al*,[14] which evaluated subjects during pregnancy and lactation (see pregnancy component above) and 2 additional publications by Anderson PO, *et. al*.[31] and LactMed.[32] The applicant did not identify any publications with use of sodium bicarbonate in lactating women.

Table 3: Published Literature with Omeprazole Use During Pregnancy and Lactation

Author/ Year	Type of Study	N Exposed/unexposed	Outcomes
Nava-Ocampo AA, et.al 2006.[14]	A meta-analysis on use of PPIs during lactation (Pregnancy is previously reported)	593 cases PPIs 534 cases on omeprazole	A 41-year-old woman started omeprazole (20mg/day) during the third trimester of pregnancy and continued during breastfeeding. Peak omeprazole concentrations in breast milk was 58 nM at 3 hours after ingestion of the drug, which corresponds to 3µg/kg/day in a breastfed infant and which was lower than 7% of the peak maternal serum concentration (950 nM at 4 h), suggesting low presence in the milk. The authors consider that all omeprazole ingested from milk would probably be destroyed in the stomach of the infant prior to absorption.
Thélin CS, *et.al* 2020[13]	A review publication evaluating publications between 1966 and 2019		There are limited data available on use of PPIs during lactation. Maternal omeprazole doses of 20 mg daily produces low levels in milk (20 µg/L found at 3 hours after dose intake). In comparison, doses at 1 mg/kg have been used in neonates. At this dose, omeprazole is not expected to cause adverse effects in infants.
Anderson PO, et. al. 2018[14] ,	A review publication		Omeprazole data consist of only one case in which the peak milk level was 20 mcg/L. All PPIs have been used safely in neonates and infants. The amounts of pantoprazole and omeprazole excreted into milk are 300–600 times less than doses reportedly given to neonates. Stomach acid degrades PPIs. Therefore, any drug in breast milk is likely to be destroyed in the infant's stomach and not systemically absorbed.

[13] Thélin CS, Richter JE. Review article: the management of heartburn during pregnancy and lactation. Aliment Pharmacol Therap. 2020;51:421–434.

[14] Anderson PO. Treating gastroesophageal reflux and heartburn while breastfeeding. Breastfeeding Med. 2018;13:463-464.

Author/ Year	Type of Study	N Exposed/unexposed	Outcomes
LactMed[15]			LactMed states: Limited information indicates that maternal omeprazole doses of 20 mg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants. Maternal Levels: A woman taking oral omeprazole 20 mg daily for gastroesophageal reflux had omeprazole measured in her milk 3 weeks postpartum. The milk omeprazole level was not detectable for 90 minutes after the dose and then reached a peak of 20 mcg/L at 3 hours after the dose. Using the peak milk level in this patient, the maximum dose that an exclusively breastfed infant would receive in breastmilk would be 3 mcg/kg daily or about 0.9% of the maternal weight-adjusted dosage. For comparison, doses of 1 mg/kg daily have been used in neonates. Infant Levels. Relevant published information was not found.

DPMH's Review of Literature

DPMH conducted a search of published literature using PubMed and Embase, Drugs in Pregnancy and Lactation by Briggs and Freeman and Medications and Mothers' Milk by Thomas Hale regarding omeprazole and/or sodium bicarbonate exposure during lactation. No new publications were identified. The reader is referred to previous reviews of omeprazole and sodium bicarbonate by Christos Mastroyannis, M.D.[1]

Review of Pharmacovigilance Database

Omeprazole/sodium bicarbonate for Oral Suspension is marketed neither in the US nor outside of the U.S.; therefore, a PV database has not yet been established.

Summary

Limited information from one case report suggests that maternal omeprazole dose of 20 mg oral daily results in low levels of omeprazole in milk. DPMH recommends that the *Lactation* subsection of Omeprazole/sodium bicarbonate for Oral Suspension labeling should state the following: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Omeprazole/sodium bicarbonate for Oral Suspension and any potential adverse effects on the breastfed infant from Omeprazole/sodium bicarbonate for Oral Suspension or from the underlying maternal condition."

[15] Drugs and Lactation Database (LactMed) [Internet]. Bethesda, MD: National Library of Medicine (US); 2006. Omeprazole. [Updated 2019 Jun 03] https://www.ncbi nlm.nih.gov/books/NBK501242/. Accessed

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Several nonclinical reproductive studies in rats and rabbits on the effects of omeprazole and other PPIs following high multiple doses did not reveal any effects on fertility. No animal studies exist on the effects of sodium bicarbonate on fertility.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature on the effects of omeprazole and/or sodium bicarbonate exposure on females and males of reproductive potential, using the following search terms:

"omeprazole" [MeSH] AND/OR "sodium bicarbonate" [MeSH] OR "proton pump inhibitor" [tiab] OR "female fertility" [MeSH] OR "male fertility" [MeSH] OR "infertility" [tiab].

The reader is referred to the applicant's submission "Response to IR" of May 15, 2020, for the complete search criteria. This search revealed 4 publications. See Table 4 below for the referenced publications.

Table 5: Published Literature with Omeprazole Effects on Females and Males of Reproductive Potential

Author/ Year	Type of Study	N Exposed/unexposed	Outcomes
Huijgen NA, *et. al,* 2016[16]	Case-control study of a population-based registry, between 1996 and 2013 from the Integrated Primary Care Information database in the Netherlands. To determine associations between proton-pump inhibitor (PPI) use and semen parameters in young men of couples who are planning pregnancy.	2,473 men from couples planning pregnancy with exposure to PPIs and with a recorded semen analysis: 241 with a low total motile sperm count (TMSC %1) and 714 with TMSC >1 as matched control.	Use of PPIs in the period between 12 and 6 months before semen analysis was associated with a threefold higher risk of low TMSC (odds ratio 2.96; 95% confidence interval [1.26–6.97]) adjusted for age and other medication. Use of PPIs during the 6 months immediately before the semen analysis was not statistically significantly associated with low TMSC.
Keihani S, *et. al* 2018[17]	A retrospective case control study from 2003 to 2013. Whether PPI use was associated with detrimental effects on semen parameters in sub-fertile men.	12,257 sub-fertile men. Patients who reported using any PPIs for >3 months before semen sample collection were included. 7698 sub-fertile men taking no medication served as controls. A total of 248 patients (258 samples) used PPIs for at least 3 months before semen collection.	PPI use (either as the only medication or when used in combination with other nonspermatotoxic medications) was not associated with statistically significant changes in semen parameters.

[16] Huijgen NA, de Ridder MAJ, Verhamme KM, et al. Are proton-pump inhibitors harmful for the semen quality of men in couples who are planning pregnancy? Fertil Steril. 2016;106(7):1666-1672.
[17] Keihani S, Craig JR, Zhang C, et al. Proton pump inhibitor use does not affect semen quality in subfertile men. Asian J Andrology. 2018;20:290–293.

Author/ Year	Type of Study	N Exposed/unexposed	Outcomes
El-Garem Y, et. al, 2014[18]	A case study to assess the effect of treatment of seminal Helicobacter pylori in infertile asthenozoospermic men.	223 infertile asthenozoospermic men. Infertile men with high seminal H pylori IgA were subjected to triple drug treatment, omeprazole, 20 mg; tinidazole, 500 mg; and clarithromycin, 250 mg twice a day for 2 weeks. Semen analysis as well as H pylori IgA antibodies was estimated after 3 months.	22 of 223 men (9.87%) demonstrated H pylori IgA antibodies in their seminal plasma. After treatment, mean seminal H pylori IgA levels demonstrated significant decrease (1.55 ± 0.4 vs 0.52 ± 0.26; 95% confidence interval, 0.83-1.21; P = 0.001) concomitant with improved progressive as well as nonprogressive sperm motility. H pylori IgA antibodies demonstrated significant negative correlation with progressive sperm motility, nonprogressive sperm motility, normal sperm morphology, and significant positive correlation with immotile sperm motility

Review of Pharmacovigilance Database

The applicant did not identify any pharmacovigilance reports of infertility with omeprazole and/or sodium bicarbonate exposure on females and males of reproductive potential.

DPMH's Review of Literature

DPMH identified 3 publications that suggest positive effects of sodium bicarbonate on vaginal pH and sperm capacitation. Bicarbonate and carbon dioxide are common components in the secretions of the female reproductive tract, especially the oviduct. At physiologic concentrations, they are believed to play an important role in sperm hyperactivation and capacitation. An improvement of cervical mucus viscoelasticity and sperm penetration following vaginal douching with sodium bicarbonate has been reported.[19,20,21]

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[18] El-Garem Y, El-Sawy M, Mostafa T. Seminal Helicobacter pylori treatment improves sperm motility in infertile asthenozoospermic men. Urology. 2014;84(6):1347-1350.

[19] Everhardt E, Dony JM, Jansen H, Lemmens WA, Doesburg WH. Improvement of cervical mucus viscoelasticity and sperm penetration with sodium bicarbonate douching. Hum Reprod 1990;5:133-7

[20] Brackett BG, Mastroianni I. Composition of oviductal fluid. In: Johnson AD, Foley CW, eds. The Oviduct and its Functions. New York, NY: Academic Press, Inc. 1974:135-99

[21] Everhardt E, Dony JM, Jansen H, Lemmens WA, Doesburg WH: Improvement of cervical mucus viscoelasticity and sperm penetration with sodium bicarbonate douching. Hum Reprod 5:133-7, 1990

DISCUSSION AND CONCLUSIONS

Pregnancy

Prolonged experience with omeprazole use during pregnancy over several decades, based on published observational studies and postmarketing reports, have not identified a drug-associated risk of major congenital anomalies, miscarriage or other adverse pregnancy outcomes with first trimester omeprazole use.

Cholestasis occurs during pregnancy in absence of omeprazole. A study by Zhang Y, *et al.*, evaluating FDA's adverse reports (FAERS and AERS) found a 2.6 times increase in cholestasis in patients using omeprazole which was further increased in pregnancy. Limitations of this study include that data in FAERS/AERS may over-represent patients with adverse effects and overlook patients who didn't experience adverse effects when using a drug. More studies are needed to further elucidate this adverse reaction in order to be considered to be included in the labeling.

A review of the literature for relevant data revealed no new safety concerns with sodium bicarbonate used in pregnant women. See below for DPMH recommendations for the omeprazole / sodium bicarbonate labeling.

Lactation

A review of the literature for relevant data revealed no new safety concerns with omeprazole or sodium bicarbonate use in lactating women. DPMH recommends the standard risk-benefit statement for breastfeeding be added to subsection 8.2 of omeprazole / sodium bicarbonate labeling.

Females and Males of Reproductive Potential

Pregnancy Testing and Contraception

Based on the above review, the available human data do not support a clear conclusion on an increased risk of major congenital malformations with use of omeprazole during pregnancy. Therefore, no labeling recommendations for pregnancy testing or contraception use are suggested for the Omeprazole/sodium bicarbonate for Oral Suspension labeling.

Infertility

A review of the literature for relevant data revealed no data on omeprazole or sodium bicarbonate effects on human fertility. Section 8.3 is not required, so is omitted.

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Appendix 1
Table 1: Published Literature with Omeprazole Exposure during Pregnancy

Author/ Year	Type of Study	N Exposed/unexposed	Outcomes
Diav-Citrin *et. al* 2005[22]	A prospective, controlled, multicenter study (8 centers) of the European Network of Teratology Information Services.	295 pregnancies exposed to omeprazole [233 in the first trimester]; compared to 868 European Network of Teratology Information Services controls counselled for non-teratogens.	Major congenital anomalies did not differ between the exposed and control groups [omeprazole 9 of 249 live births (3.6%), vs. controls 30 of 792 (3.8%]. No differences were found when exposure was limited to the first trimester after exclusion of genetic, cytogenetic or infectious anomalies. Miscarriage: Omeprazole 24 of 296 (8.1%) vs controls 58 of 868 (6.7%) Stillbirth: Omeprazole 3 of 296 deliveries (1.0) vs controls 2 of 868 (0.2%) Conclusions: "Proton pump inhibitors do not represent a major teratogenic risk in humans."
Källén BAJ. 2001[23]	Case control. Infants whose mothers used omeprazole during pregnancy were identified from the Swedish Medical Birth Registry Delivery outcome was studied: presence of congenital malformations, perinatal survival, low birth weight, low Apgar score and hospitalization up to the end of 1997.	A total of 955 exposed infants born in 1995-1999 were identified: 863 of which were exposed in early pregnancy and 131 later in pregnancy and 39 who had been exposed both in early and late pregnancy.	Results: No clear-cut indication of ill effects were seen. Five infants were stillborn. The odds ratio for having any malformation, stratified for year of birth, maternal age, parity, and maternal smoking in early pregnancy is 0.82 (95% confidence interval [CI 0.50-1.34]). The rate of congenital heart defects was slightly increased, but both effects may be random. Conclusions: "The present dataset and previously published data give no reason for concern after exposure for omeprazole during pregnancy."
Pasternak B, Hviid A. 2010[24]	A cohort study of all infants born alive in Denmark between January 1996 and September 2008. Linked data from nationwide registries.	Among 840,968 live births, 5082 involved exposure to PPIs between 4 weeks before conception and the end of the first trimester of pregnancy.	174 major birth defects in infants whose mothers had been exposed to PPIs during this period (3.4%), as compared with 21,811 in the group whose mothers had not been exposed (2.6%) (adjusted prevalence odds ratio, 1.23; 95% CI, [1.05 to 1.44]). In analyses limited to exposure during the first trimester, there were 118 major birth defects among 3651 infants exposed to PPIs (3.2%), and the adjusted prevalence odds ratio was 1.10 (95% CI, [0.91 to 1.34]). The risk of birth defects was not significantly increased in secondary analyses of exposure to individual PPIs during the first trimester

[22] Diav-Citrin O, Arnon J, Shechtman S, et al. The safety of proton pump inhibitors in pregnancy: a multicenter prospective controlled study. Aliment Pharmacol Therap. 2005;21:269–275.

[23] Källén BAJ. Use of omeprazole during pregnancy – no hazard demonstrated in 955 infants exposed during pregnancy. Eur Obstet Gynecol Reprod Biol. 2001;96(1):63-68.

[24] Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. N Engl J Med. 2010;363:2114–2123.

Matok I, *et. al* 2012[25]	Database study that assessed the fetal safety of PPIs following exposure during gestation, including data from medical pregnancy terminations. A unified computerized database was created by linking a computerized database of medications dispensed from 1998 to 2009 to all women registered in ‘‘Clalit’’ HMO, with computerized databases containing maternal and infant hospitalization records from the district hospital.	A total of 114,960 (75%) infants were born during the study period to women registered at ‘‘Clalit,’’ 110,783 of them were singleton pregnancies; 1,239 women had medical pregnancy terminations, of which 468 were performed due to fetal malformations. A total of 1,186 infants and abortuses had been exposed to PPIs during the first trimester of pregnancy	Exposure to PPIs was not associated with an increased risk of congenital malformations (adjusted OR 1.06; 95% CI = 0.84–1.33). Similarly, exposure to PPIs during the third trimester of pregnancy was not associated with increased risk of perinatal mortality, premature delivery, low birth weight, or low Apgar scores.
Zhang Y, *et. al* 2019[26]	A retrospective cohort study Analyzed ~ 9.5 million FDA adverse effect reports to identify drugs with increasing risks of cholestasis as an adverse effect.	The cholestasis cohort contained 17,385 records and the non-cholestasis cohort contained 9,408,128 records.	The odds ratio analysis reveals that omeprazole is associated with an increased risk of cholestasis by a factor of 2.61 [2.54, 2.69]. The risk of cholestasis associated with omeprazole is further increased in pregnant women.
Nikfar S, *et. al* 2002[27]	A meta-analysis of 5 cohort studies. All included studies were pooled and weighted. Cohort studies ascertained pregnancy outcome with either registry linkage or by direct interview with the mother.	With 593 exposed pregnancies vs 15,330 unexposed pregnancies	The overall relative risk was 1.18 with a 95% CI of 0.72–1.94. In conclusion, proton pump inhibitors do not present a major teratogenic risk when used in recommend doses.

[25] Matok I, Levy A, Wiznitzer A, Uziel E, Koren G, Gorodischer R. The safety of fetal exposure to proton-pump inhibitors during pregnancy. Dig Dis Sci. (2012) 57:699–705.

[26] Zhang Y, Shi D, Abagyan R, Dai W, Dong M. Population scale retrospective analysis reveals potential risk of cholestasis in pregnant women taking for omeprazole, lansoprazole, and amoxicillin. Interdiscip Sci. 2019;11(2):273–281.

[27] Nikfar S, Abdollahi M, Moretti ME, Magee LA, Koren G. Use of proton pump inhibitors during pregnancy and rates of major malformations. A meta-analysis. Dig Dis Sci. 2002;47:1526–1529.

Richter JE, *et. al* 2005[28]	A review publication		The weight of evidence suggests omeprazole is safe in pregnancy. Omeprazole is classified as a class C drug in pregnancy because at doses similar to those used in humans, omeprazole produced dose-related embryonic and fetal mortality in pregnant rats and rabbits. No teratogenicity was observed. The FDA has received reports of at least 12 birth defects in pregnant women exposed to omeprazole, including anencephaly and hydrocephaly.
Nava-Ocampo AA, *et.al* 2006[29]	A multicenter prospective cohort study conducted by Motherisk	113 mothers exposed to omeprazole during pregnancy, including 101 mothers exposed during organogenesis. Two control groups were used: a disease-paired control group using histamine H_2-blockers and a control group of healthy women exposed to nonteratogenic medications.	The rate of major malformations in the omeprazole group (5%) did not differ significantly from rates in the nonteratogenic drug control group (3%) and in the disease-paired control group (3%). Rates of spontaneous abortions, preterm deliveries, cesarean sections, and neonatal health problems; birth weight; and gestational age at delivery were also comparable in the 3 groups.
Nava-Ocampo AA, et.al 2006. Same publication	A meta-analysis on use of PPIs during pregnancy	593 cases PPIs 534 cases on omeprazole	All exposures to PPIs had a relative risk of 1.18 (95% confidence interval [CI] 0.72 to 1.94) and exposures to omeprazole only had a relative risk of 1.05 (95% CI 0.59 to 1.85), indicating no increase in risk of malformations. Conclusion: Overall, a rule of thumb during pregnancy is to choose an older agent in a pharmacologic class for which there are more fetal safety data that indicate the medication is effective. Applying this rule to PPIs makes omeprazole the drug of choice for now.

[28] Richter JE. Review article: the management of heartburn in pregnancy. Alimentary Pharmacol Therap. 2005;22(9):749-757.
[29] Nava-Ocampo AA, Valazquez-Armenta EY, Han J-Y, Koren G. Use of proton pump inhibitors during pregnancy and breastfeeding. Can Fam Physician. 2006;52:853-854.

Li CM, *et. al* 2010[30]	A meta analysis of 20 cohort and 6 case control studies Outcomes included congenital malformations, abortion, stillbirth, neonatal death, preterm birth, small for gestational age and low birth weight.		Pooled odds ratios (OR) and 95% CI were obtained by random-effects modelling. PPI use was associated with an increased risk of congenital malformations (OR 1.28, 95% CI 1.09-1.52), especially in case-control studies (OR 2.04, 1.46-2.86). No significant associations were found between PPI use and abortions, stillbirth, neonatal death, preterm birth and low-birth weight.
Gill SK, *et. al* 2009[31]	A meta analysis from inception of PPIs until 2008. 7 Publications	134,940 patients, including 1,530 exposed and 133,410 not exposed to PPIs	The overall odds ratio (OR) for major malformations was 1.12 (95 % confidence interval, CI: 0.86 – 1.45). Further analysis revealed no increased risk for spontaneous abortions (OR = 1.29, 95 % CI: 0.84 – 1.97); similarly, there was no increased risk for preterm delivery (OR = 1.13, 95 % CI: 0.96 – 1.33). In the secondary analysis of 1,341 exposed and 120,137 not exposed to omeprazole alone, the OR and 95 % CI for major malformations were 1.17 and (0.90 – 1.53), respectively. Conclusion: On the basis of these results, PPIs are not associated with an increased risk for major congenital birth defects, spontaneous abortions, or preterm delivery. The narrow range of 95 % CIs is further reassuring, suggesting that PPIs can be safely used in pregnancy.
Lai T, *et. al* 2018[32]	A meta analysis of 8 observational (retrospective cohort, case control and case-crossover studies) studies. All the studies were pooled		Acid-suppressive drug use in pregnancy was associated with an increased risk of asthma in childhood (relative risk [RR] = 1.45; 95% confidence interval [CI] 1.35–1.56; I2 = 0%; P < .00001). The overall risk of asthma in childhood increased among proton pump inhibitor users (RR = 1.34; 95% CI (1.18–1.52); (P < .00001). Limitations: No adjustment for known confounders
Thélin CS, *et.al* 2020[33]	A review publication evaluating publications between 1966 and 2019		PPIs are reserved for pregnant and lactating women with intractable symptoms or complicated GERD; Overall, there is evidence that while birth defects, including cardiac defects, have been reported in pregnancies exposed to a PPI, there is no evidence of a causal association. Reviews have concluded that PPIs can be used in pregnancy with relative safety. Thus, the current data suggests that omeprazole at doses 20-60 mg/d, even in the first trimester of pregnancy, can be classified as low risk.

[30] Li CM, Zhernakova A, Engstrand L, Wijmenga C, Brusselaers N. Systematic review with meta-analysis: the risks of proton pump inhibitors during pregnancy. Aliment Pharmacol Therap. 2010;51:410–420.

[31] Gill SK, O'Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. Am J Gastroenterol. 2009;104:1541–1545.

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Erichsen R, *et. al* 2014[34]	A population-based prevalence study including all live-born boys from 1997 through 2009 using Danish nationwide registries, with hospital diagnosed hypospadias	430,569 live-born boys of whom 2926 were exposed to maternal PPI use during early pregnancy, whereas 2683 were unexposed A total of 5227 boys were exposed during the entire pregnancy. Overall hypospadias after exposure to omeprazole during 1st trimester: n=5, APR*=1.2 (0.6-2.2) while overall hypospadias after exposure during the whole pregnancy: n=10, APR=1.0 (0.6-1.5) *Adjusted Prevalence Ratio	Incidence of hypospadias after maternal PPI use through first trimester or thoughout pregnancy. Among the exposed boys, 20 (0.7%) were diagnosed with hypospadias, whereas 2683 (0.6%) of the nonexposed had hypospadias (adjusted prevalence ratio = 1.1; 95% confidence interval, [0.7–1.7]). Of 5227 boys who were exposed during the entire pregnancy, 32(0.6%) had hypospadias corresponding to a prevalence ratio of 1.0 (95% confidence interval, [0.7–1.4]). The sub-analysis restricted to omeprazole exposure showed similar results [1.6 (95% CI, 0.7–3.9)]. The authors concluded that maternal PPI use during pregnancy was not associated with hypospadias in boy offspring.

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