CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213593Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA Resubmission to Complete Response
Application Number(s)	NDA 213593/Original-1 (b) (4)
Priority or Standard	Standard, Class 2 Resubmission
Submission Date (Initial)	March 30, 2020
Received Date (Initial)	March 30, 2020
Complete Response Action Date (Initial)	January 30, 2021
Submission Date (Resubmission)	March 4, 2022
Received Date (Resubmission)	March 4, 2022
PDUFA Goal Date (Resubmission)	September 4, 2022
Action Goal Date (Resubmission)	August 30, 2022
Division/Office	Division of Gastroenterology Office of Inflammation and Immunology
Review Completion Date	August 30, 2022
Established/Proper Name	Omeprazole and Sodium Bicarbonate
(Proposed) Trade Name	Konvomep
Pharmacologic Class	Proton Pump Inhibitor
Code name	None
Applicant	Azurity Pharmaceuticals, Inc
Dosage form	For Oral Suspension
Applicant proposed Dosing Regimen	Refer to Section 1.1, Table 2
Applicant Proposed Indication(s)/Population(s)	In adults for: (b) (4) 2) Short-term treatment (4 to 8 weeks) of active benign gastric ulcer (b) (4)

	[redacted] 7) Reduction of risk of upper gastrointestinal (GI) bleeding in critically ill adult patients
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	[redacted] Gastric Ulcer [redacted] Gastrointestinal Hemorrhage
Recommendation on Regulatory Action	[Original-1]: Approval [redacted]
Recommended Indication(s)/Population(s) (if applicable)	In adults for: 1) Short-term treatment (4 to 8 weeks) of active benign gastric ulcer 2) Reduction of risk of upper GI bleeding in critically ill adult patients
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Gastric Ulcer Gastrointestinal Hemorrhage
Recommended Dosing Regimen	1) Active Benign Gastric Ulcer: 40 mg once daily for 4 to 8 weeks 2) Reduction of Risk of Upper GI Bleeding in Critically Ill Patients: 40 mg initially followed by 40 mg 6 to 8 hours later and 40 mg once daily thereafter for 14 days

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Abbreviations: DG, Division of Gastroenterology; OCP, Office of Clinical Pharmacology

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Abbreviations: ATL, application technical lead; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DPMH, Division of Pediatric and Maternal Health; DPV, Division of Pharmacovigilance; DRM, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Signatures

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ANDA	abbreviated new drug application
$AUC_{0\text{-}inf}$	area under the plasma concentration versus time curve extrapolated to infinity
$AUC_{0\text{-}t}$	area under the plasma concentration to the last measurable concentration
AUC	area under the plasma concentration versus time curve
BA	bioavailability
BE	bioequivalence
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CR	complete response
DMF	drug master file
DR	discipline review
EE	erosive esophagitis
FDA	Food and Drug Administration
GERD	gastroesophageal reflux disease
GI	gastrointestinal
H_2RA	histamine-2 receptor antagonist
LD	listed drug
NDA	new drug application
NG	nasogastric
NSAID	nonsteroidal anti-inflammatory drug
OCP	Office of Clinical Pharmacology
OG	orogastric
OPQ	Office of Pharmaceutical Quality
PI	prescribing information
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PUD	peptic ulcer disease
SLC	safety labeling changes
USP	United States Pharmacopeia

1. Executive Summary

1.1. Product Introduction

Proposed trade name: Konvomep

Generic name: Omeprazole and sodium bicarbonate for oral suspension

Pharmacologic class: Proton pump inhibitor (PPI)

Route of administration, description, and formulation: Konvomep (omeprazole and sodium bicarbonate for oral suspension) is a fixed-dose combination product that is supplied as a kit. Each kit is comprised of one bottle of omeprazole powder and one bottle of strawberry-flavored diluent containing sodium bicarbonate. Konvomep is for reconstitution by a healthcare provider prior to dispensing to a patient. Three package sizes are proposed, as noted in Table 1 below.

Table 1. Proposed Konvomep (Omeprazole and Sodium Bicarbonate for Oral Suspension) Package Sizes and Contents

Final Volume of Konvomep After Reconstitution	Kit Contents: One Bottle Omeprazole Powder and One Bottle Diluent Containing Sodium Bicarbonate
90 mL	0.18 g omeprazole powder 7.56 g sodium bicarbonate per 90 mL
150 mL	0.3 g omeprazole powder 12.6 g sodium bicarbonate per 150 mL
300 mL	0.6 g omeprazole powder 25.2 g sodium bicarbonate per 300 mL

Source: Reviewer's Table.

When constituted, the oral suspension contains the equivalent of 2 mg/mL of omeprazole and 84 mg/mL of sodium bicarbonate:

(b) (4)

- 20 mL of the constituted product provides an oral dose of 40 mg of omeprazole and 1680 mg of sodium bicarbonate

New Drug Application (NDA) Submission

In this NDA, the Applicant has proposed to rely upon the FDA's findings of safety and effectiveness for the following listed drugs (LDs) under the 505(b)(2) pathway:

(1) Zegerid (omeprazole and sodium bicarbonate) for oral suspension (NDA 021636)
(2) Prilosec (omeprazole) delayed-release capsules (NDA 019810)

Although the Applicant included Prilosec as a LD, all the information regarding FDA's findings of safety and effectiveness upon which the Applicant has proposed to rely is contained in the prescribing information (PI) for Zegerid for oral suspension (NDA 021636) (Salix 2022).

Similar to the LD, Zegerid, Konvomep is a fixed-dose combination product. Sodium bicarbonate is considered an active ingredient, as it acts as an acid neutralizing agent to reduce acid degradation of omeprazole in the stomach to permit absorption of omeprazole.

Konvomep contains the same amount of omeprazole and sodium bicarbonate as the LD, Zegerid, at the higher dose of 40 mg/1680 mg. (b) (4)

No clinical efficacy studies were conducted to support this NDA. The Applicant conducted two relative bioavailability (BA) studies to establish a bridge between the proposed drug product and the LD.

(1) Study OME-RM02-001: a single-dose, three-arm, fasted state, relative BA study of the proposed Konvomep (omeprazole and sodium bicarbonate for oral suspension), 40 mg/1680 mg; Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 40 mg/1680 mg; and Prilosec (omeprazole) delayed-release capsules, 40 mg (Sandoz, abbreviated new drug application [ANDA] 076515, Reference Standard per Orange Book).

    This study was submitted and reviewed in the initial NDA, which received a complete response (CR) on January 28, 2021.

(2) Study 5032423: a single-dose, two-arm, relative BA study of Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 20 mg/1680 mg and Konvomep (omeprazole and sodium bicarbonate) for oral suspension, 20 mg/840 mg. This study is submitted in this NDA resubmission.

(b) (4)
Table 2 includes the Applicant's proposed dosage regimens by indication.

Table 2. Applicant's Proposed Dosage Regimen of Konvomep (Omeprazole and Sodium Bicarbonate for Oral Suspension) for Adults by Indication

Indication	Recommended Dosage	Treatment Duration
(b) (4)		
Treatment of Benign Gastric Ulcer	40 mg once daily	4 to 8 weeks
(b) (4)		
Reduction of Risk of Upper GI Bleeding in Critically Ill Patients	40 mg initially; followed by 40 mg 6 to 8 hours later; and 40 mg once daily thereafter	14 days
(b) (4)		

Source: NDA submission: Table 1 of Draft Labeling, Konvomep, submitted March 4, 2022.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The initial submission of NDA 213593 was on March 30, 2020, and this application received a CR on January 28, 2021. The CR action was taken for the following reasons: Chemistry, manufacturing, and controls (CMC) and manufacturing deficiencies for Konvomep (omeprazole and sodium bicarbonate for oral suspension), (b) (4) (b) (4) and lack of data to support administration via nasogastric/ orogastric (NG/OG) tube (relevant to the 40 mg/1680 mg Konvomep dose and the proposed indication of reduction of risk of upper gastrointestinal bleeding in critically ill patients).

The review team relayed the following clinical deficiency to the Applicant in the January 28, 2021, CR Letter regarding the (b) (4)

(b) (4)

In response to the CR Letter, the Applicant submitted the NDA resubmission on March 4, 2022. Within the resubmission, the Applicant has addressed the product quality deficiencies and provided information to demonstrate that the proposed control strategies for the omeprazole and sodium bicarbonate active pharmaceutical ingredients of the fixed-dose combination product meet the regulatory standard. The resubmission also provided data from an in vitro

NG/OG tube study to support the NG/OG route of administration for Konvomep, which is the recommended route of administration of the drug for the indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients." These data were evaluated by the Office of Pharmaceutical Quality (OPQ) and found to be acceptable. See Section 4.2 for additional details.

During the review of the resubmission, the review team identified issues that led to the administrative split of the application into NDA 213593/Original-1; Konvomep (omeprazole and sodium bicarbonate for oral suspension), 40 mg/1680 mg (b) (4) These are discussed separately below.

NDA 213593/Original-1

Although a scientific bridge was established for the proposed 40-mg/1680-mg dose of Konvomep and the LD, Zegerid, 40-mg/1680-mg dose during the review of the original NDA (see review dated January 28, 2021), CMC deficiencies precluded approval of Konvomep at that time. In the initial March 30, 2020 NDA submission, the Applicant provided results of a relative BA study (OME-RM02-001) that demonstrated that administration of Konvomep, 40 mg/1680 mg resulted in systemic omeprazole exposures for both maximum plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) that were comparable to the LD, Zegerid, 40 mg/1680 mg (NDA 021636) by meeting recommended bioequivalence criteria (March 2014). Of note, the comparability of the sodium bicarbonate component in Konvomep to the LD, Zegerid, was assessed by the ability of the sodium bicarbonate to prevent the degradation of omeprazole, which allows for the systemic absorption of omeprazole and was demonstrated in Study OME-RM02-001 by the comparable C_{max} and AUC of omeprazole between Konvomep and Zegerid.

The CMC deficiencies identified during the prior review have been adequately addressed in this resubmission, which supports the following treatment indications in adults:

- Short-term treatment (4 to 8 weeks) of active benign gastric ulcer
- Reduction of risk of upper gastrointestinal (GI) bleeding in critically ill adult patients

The recommended dosage regimen by indication is summarized in Table 3 below. The recommended dosage is based upon the omeprazole content of Konvomep.

Table 3. Recommended Dosage Regimen of Konvomep for Adults by Indication

Indication	Recommended Dosage (Based on Omeprazole Content)	Treatment Duration
Treatment of benign gastric ulcer	40 mg once daily	4 to 8 weeks
Reduction of risk of upper GI bleeding in critically ill patients	40 mg initially; followed by 40 mg 6 to 8 hours later; and 40 mg once daily thereafter	14 days

Source: Adapted from Applicant's Proposed PI for Konvomep, submitted July 18, 2022.

ulti-disciplinary Review and Evaluation

NDA 213593/Original-1 was reviewed by a multidisciplinary review team. Through reliance on the FDA's findings of safety and effectiveness for the LD, Zegerid 40 mg/1680 mg, the overall benefit-risk was found to be favorable for the Konvomep, 40 mg/1680 mg (as described in the Benefit-Risk Framework below). With resolution of the product quality deficiencies identified during the initial NDA review and communicated in the January 28, 2021, CR letter, all disciplines recommended approval of Konvomep, 40 mg/1680 mg in this review cycle.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Acid-mediated gastrointestinal diseases (e.g., active gastric and duodenal ulcers, erosive esophagitis, risk of upper gastrointestinal bleeding in critically ill patients) are common conditions that can have serious complications, affect quality of life, and may require long-term treatment. Proton pump inhibitors (PPIs) are first line treatments and are highly effective for these conditions. Konvomep (omeprazole and sodium bicarbonate for oral suspension) is a PPI that offers an alternative treatment option and may benefit adult patients who cannot swallow oral tablets/capsules, or who need medication via a nasogastric/orogastric (NG/OG) tube.

No clinical safety or efficacy studies with Konvomep were conducted.

NDA 213593/Original-1

A scientific bridge was established for the Konvomep, 40-mg/1680-mg dose through the demonstration of comparable bioavailability (BA) and supports the Applicant's reliance upon the FDA's findings of safety and effectiveness for the listed drug (LD), Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 40 mg/1680 mg (new drug application [NDA] 021636). Approval is recommended for Konvomep, 40 mg/1680 mg for the indications in adults of the treatment of active benign gastric ulcer and the reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients.

(b) (4)

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The goals of managing acid-mediated GI conditions are to relieve the symptoms and prevent complications by reducing esophageal, gastric, and duodenal exposure to acid. Treatments include lifestyle modifications, pharmacological management, or surgical treatments. • Standard of care pharmacological management of acid-mediated GI conditions includes treatment with histamine-2 receptor antagonists (H_2RAs), proton pump inhibitors (PPIs), cytoprotectants (e.g., sucralfate), and treatment of *H. pylori* infection (when present). Proton pump inhibitors and *H. pylori* eradication are the typically the most effective treatment for these conditions. • In general, PPIs are well tolerated; however, there is extensive off-label and long-term use. Multiple safety issues have been identified, often associated with higher doses and/or longer duration of use, as included in the Warning and Precautions Sections of the prescribing information (PI) of PPIs.	• There are many approved, safe, and effective therapies; however, due to the widespread impact and potentially serious long-term effects, there is a need to develop additional safe and effective treatments for acid-mediated GI conditions. • Konvomep (omeprazole and sodium bicarbonate for oral suspension) is a PPI that can be administered to adult patients who experience difficulty in swallowing or need mediations administered by NG/OG tube.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	**Original-1** • Results from a relative BA study (Study OME-RM02-001) indicate that Konvomep, 40 mg/840 mg has comparable omeprazole systemic exposure (area under the plasma concentration versus time curve [AUC] and maximum plasma concentration [C_{max}]) to Zegerid for oral suspension, 40 mg/1680 mg. The 90% CI for the ratio of the geometric means of AUC_{0-t}, AUC_{inf} and C_{max} were within the recommended bioequivalence criteria of 80-125%. • An in vitro study of nasogastric/orogastric (NG/OG) tubes demonstrated compatibility of the tubes with the Konvomep suspension and drug recovery was similar before and after the suspension was pushed through the tubes for tube sizes ≥ 8 French. [redacted] (b) (4)	**Original-1** • A scientific bridge has been established between Konvomep, 40 mg/840 mg and the LD, Zegerid, 40 mg/1680 mg. This bridge is adequate to justify the Applicant's proposed reliance upon FDA's findings for the safety and effectiveness for Zegerid for the indications approved for the 40 mg/1680 mg dosage. • The NG/OG tube study results are adequate to support administration of Konvomep suspension via tubes 8 French and larger and the indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients." • No therapeutic advantage of Konvomep over other approved omeprazole; and omeprazole and sodium bicarbonate-containing products; or other PPIs has been identified; however, the oral suspension formulation is an additional treatment option for the proposed acid-related GI indications, especially for adult patients who cannot swallow oral tablets/capsules or require a NG/OG tube.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	[redacted] (b) (4)	
Risk and Risk Management	• Product quality concerns in the original NDA submission have been addressed. **Original-1** • Few adverse events were reported following a single dose to healthy volunteers in Study OME-RM02-001. See the initial review of NDA 213593 dated March 30, 2020. • The safety profile of Konvomep, 40 mg/1680 mg is expected to be similar to Zegerid, 40 mg/1680 mg. • Common adverse reactions reported with Zegerid are headache, abdominal pain, nausea, diarrhea, vomiting and flatulence. • Serious and otherwise clinically significant adverse reactions reported with the PPI-class of drugs, including omeprazole, includes acute tubulointerstitial nephritis, *Clostridioides difficile*-induced diarrhea, bone fracture, severe cutaneous adverse reactions,	• The Applicant provided adequate chemistry, manufacturing, and controls (CMC) information to ensure the identity, strength, purity, and quality of the proposed drug product. **Original-1** • No new safety concerns were identified. • Known risks associated with the PPIs will be addressed through product labeling. • Routine pharmacovigilance is recommended. • No risk management strategy is needed. • No postmarketing commitment, postmarketing requirement, or risk evaluation and mitigation strategy is recommended.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cutaneous and systemic lupus erythematosus, and fundic gland polyps. Some of these adverse reactions are known to be associated with dose and/or duration of PPI use.	• The overall benefit-risk of Konvomep, 40 mg/1680 mg is favorable for the following treatment indications in adults: 1. Acute benign gastric ulceration 2. Reduction in risk of upper GI bleeding in critically ill patients
	[redacted] (b) (4)	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4)	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	**The patient experience data that were submitted as part of the application include:**			**Section of review where discussed, if applicable**
	□	Clinical outcome assessment (COA) data, such as		
		□	Patient-reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

(b) (4)

The section is adapted (in part) from the initial NDA 213593 unireview, dated January 28, 2021.

(b) (4)

Risk of Upper GI Bleeding in Critically Ill Patients

Most critically ill patients are at an increased risk for developing erosions and ulceration of the mucosa of the GI tract (Saeed et al. 2022). The exact physiology is not fully known, but postulated mechanisms include splanchnic and GI tract hypoperfusion, mucosal ischemia or

disruption leading to decreased mucous secretion, and increased acid production with subsequent GI tract injury. Critically ill patients are at an increased risk for developing stress ulcers of the mucosa of the upper GI tract, and subsequent GI bleeding. The beneficial effects of prophylaxis to prevent stress ulcers and GI bleeding support its routine use in critically ill patients with risk factors for developing stress ulcers (Saeed et al. 2022).

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(b) (4)

2.2. Analysis of Current Treatment Options

NDA 213593/Original -1

The goals of managing active benign gastric ulcer are to relieve symptoms and prevent complications by reducing esophageal, gastric, and duodenal exposure to acid. Treatments include lifestyle modifications, pharmacological management, or surgical treatments. Surgical intervention is reserved for intractable cases. Pharmacological management of active benign gastric ulcer includes treatment of *H. pylori* infection, H_2RAs, PPIs, and cytoprotectants such as sucralfate.

There are six approved delayed-release formulations of PPIs (i.e., omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole, and dexlansoprazole) and an immediate-release formulation of one PPI, Zegerid (omeprazole and sodium bicarbonate) for oral suspension and Zegerid (omeprazole and sodium bicarbonate) capsules. Of these, lansoprazole, esomeprazole, omeprazole, and omeprazole and sodium bicarbonate are available in over-the counter formulations. There are two FDA-approved H_2RAs (famotidine and nizatidine), both of which are available in over-the-counter formulations.

Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 40 mg/1680 mg is the only treatment that is FDA approved for the reduction of risk of upper GI bleeding in critically ill patients. Off-label treatments for gastric ulcers and for the reduction of risk of upper GI bleeding in critically ill patients include other PPIs, H_2RAs, and sucralfate (Ye et al. 2020).

(b) (4)

Table 4. Current Treatments for Acid-Mediated GI Conditions in Adult Patients, FDA Approved

Product(s) Name	Relevant Indication	Year of Initial Approval	Drug Class	Dosing/ Administration	Common Adverse Effects
Omeprazole	• Symptomatic GERD • Treatment of EE • Maintenance of healing of EE • Active duodenal ulcer • Active benign gastric ulcer • Eradication of *Helicobacter pylori* • Hypersecretory conditions	1989	PPI	Delayed-release Capsule: 10 mg, 20 mg or 40 mg Suspension: 2 mg, 5 mg, 10 mg per packet ODT tablet: 20 mg Once or twice a day	Reported ≥2% of subjects: • Headache • Abdominal pain Nausea • Vomiting • Diarrhea • Flatulence
Lansoprazole	• Active duodenal ulcer • Symptomatic GERD • Treatment of EE • Maintenance of healed duodenal ulcer • Active benign gastric ulcer • Maintenance of healing of EE • Healing of NSAID associated gastric ulcer • Eradication of *H. pylori* • Hypersecretory conditions	1995	PPI	Capsule: 30 mg, Orally disintegrating tablet: 30 mg 30 mg once daily	Reported ≥1% of subjects: • Diarrhea • Abdominal Pain Constipation • Nausea
Rabeprazole	• Symptomatic GERD • Active duodenal ulcer • Treatment of EE • Maintenance of healing of EE • Eradication of *H. pylori*	1999	PPI	Tablet: 20 mg once a day (10 mg tab discontinued)	Reported >2% in adults • Abdominal pain Constipation • Flatulence • Pharyngitis • Infection

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Product(s) Name	Relevant Indication	Year of Initial Approval	Drug Class	Dosing/ Administration	Common Adverse Effects
Pantoprazole	• Treatment of EE • Maintenance of healing of EE • Hypersecretory conditions	2000	PPI	Tablet: 20 mg or 40 mg Suspension: 40 mg IV: 40 mg/vial Orally or IV Once or twice a day	Reported >2% in adults • Headache • Abdominal pain • Diarrhea • Nausea • Vomiting • Flatulence • Dizziness • Arthralgia
Esomeprazole	• Symptomatic GERD • Healing of EE • Maintenance of healing of EE • Risk reduction of NSAID associated gastric ulcer • Eradication of *H. pylori* to reduce duodenal ulcer recurrence • Hypersecretory conditions	2001	PPI	Capsule: 20 mg, 40 mg Suspension: 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg Tablet: 20 mg (OTC) IV: 40 mg/vial Orally or IV Once or twice a day	Reported ≥1% in adults • Diarrhea • Headache • Abdominal pain • Nausea • Flatulence • Constipation • Dry mouth
Dexlansoprazole	• Symptomatic GERD • Healing of EE • Maintenance of healing of EE	2009	PPI	Capsule: 30 mg, 60 mg Orally Once a day	Reported ≥2% in adults: • Diarrhea • Abdominal pain • Nausea • URI • Vomiting • Flatulence

Product(s) Name	Relevant Indication	Year of Initial Approval	Drug Class	Dosing/ Administration	Common Adverse Effects
Omeprazole IR and sodium bicarbonate	• Active duodenal ulcer • Active benign gastric ulcer • Symptomatic GERD • Treatment of EE • Maintenance of healing of EE • Upper GI bleeding in critically ill adult patients	2004	PPI	Immediate-release Capsule: 40 mg/1100 mg For oral suspension: 40 mg/1680 mg per pkt 40 mg (omeprazole component) orally or via NG/OG once daily	Reported ≥2% of subjects: • Headache • Diarrhea • Abdominal pain • Nausea • Vomiting • Flatulence
Famotidine	• Active duodenal ulcer • Active benign gastric ulcer • Symptomatic GERD • Treatment of EE • Hypersecretory conditions • Reduction of the risk of DU recurrence	1986	H2RAs	Tablet: 10 mg, 20 mg, 40 mg Suspension: 40 mg per 5 mL IV: 10 mg/ml Once or twice a day	The most common AEs: • Headache • Dizziness • Constipation • Diarrhea
Cimetidine	Symptomatic GERD	1977	H2RAs	Tablet: 200,300, 400, 800 mg Orally (IV discontinued) Once or twice a day	The most common AEs: • Headache • Dizziness • Constipation • Diarrhea
Nizatidine	Active benign gastric ulcer	1988	H2RAs	Capsule: 150 mg twice daily, or 300 mg once daily	The most common AEs: • Headache • Dizziness • Constipation • Diarrhea • Rash • URI

Product(s) Name	Relevant Indication	Year of Initial Approval	Drug Class	Dosing/ Administration	Common Adverse Effects
Metoclopramide	Symptomatic documented GERD in patients who fail to respond conventional therapy	1980	Prokinetic	Tablet: 5 mg, 10 mg ODT: 5 mg, 10 mg Solution: 5 mg/5 mL Orally Once, twice, three, or four times a day	The most common AEs (>10%) • Restlessness • Drowsiness • Fatigue • Lassitude
Sucralfate	Active duodenal ulcer	1981	Cytoprotectant	Tablet: 1 gram Oral Suspension: 1 gram/10 mL Orally Four times a day before meals	The most common AEs (>2%) • Constipation • Nausea • Vomiting

Source: Adapted from the Clinical reviewer's table in NDA 213593 Multi-Disciplinary Integrated Clinical Review, dated January 28, 2021; and based on information accessed between May 2022 and August 2022 *Data obtained from Drugs@FDA website, U.S. Food and Drug Administration, www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Updated Daily; and https://dailymed.nlm.nih.gov/dailymed.
Another H2RA, ranitidine, has been withdrawn due to concerns that the amount of the (b) (6) impurity in the product may reach unacceptable levels during storage.
Abbreviations: AE, adverse event; DU, duodenal ulceration; EE, erosive esophagitis; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; GI, gastrointestinal; H2RA, histamine 2 receptor antagonists; IR, immediate release; mg, milligram; NDA, new drug application; NG, nasogastric; NSAID, nonsteroidal anti-inflammatory drug; ODT, orally disintegrating tablet; OG, orogastric; OTC, over-the-counter; pkt, packet; PPI, proton pump inhibitor; URI, upper respiratory infection.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

- Konvomep (omeprazole and sodium bicarbonate for oral suspension) is not approved in any country.
- The initial NDA 213593 was submitted to the Agency on March 30, 2020.
- Upon review of the initial submission, the Agency issued a CR letter on January 28, 2021 (Food and Drug Administration 2021).
- Refer to the unireview (dated January 28, 2021) for additional information regarding the initial submission.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following is a brief summary of the key regulatory interactions between the Agency and the Applicant that have occurred at and since the time of CR action of the initial NDA on January 28, 2021.

Complete Response Letter to the NDA: January 28, 2021

- The initially submitted NDA was not approved. The Agency cited product quality issues and clinical issues as the basis for issuing the CR letter.
- In general, the submission lacked sufficient information to demonstrate that the proposed control strategy for the omeprazole and sodium bicarbonate active ingredients of the combination product met the regulatory standard.
  - The strength of the active ingredient, sodium bicarbonate, in the drug product throughout the product shelf-life and during the in-use period was not adequately assured.
  - The strength and uniformity of the active ingredient omeprazole in the constituted suspension at release and on stability were not assured.
  - In-process controls for the active ingredient sodium bicarbonate assay (b) (4) were not established.

(b) (4)

(b) (4)

- Data were submitted to the application late in the review cycle demonstrate that the product could be administered via nasogastric/orogastric (NG/OG) tubes; however, these were not reviewed prior to the issuance of the CR. Lack of information on this method of administration precluded approval of the 40-mg/1680-mg Konvomep dose for the indication of reduction of risk of upper GI bleeding.

Type A, End of Review Teleconference on May 25, 2021 (Meeting Minutes Dated June 15, 2021)

- The Applicant discussed the deficiencies identified in the CR Letter with the Agency and proposed plans for addressing the deficiencies, including the stability of the diluent and the manufacturing process.
- No additional information was needed to support the indication of "reduction of risk of upper GI bleeding in critically ill patients" with the 40-mg dose. The in vitro NG/OG study should be included in the NDA resubmission. The Agency stated that a final determination regarding the adequacy of the data to support the indication will be made during the review of the resubmission of the NDA.

(b) (4)

- The Agency stated that it may be possible to draft adequate labeling for the 40-mg (b) (4) dose of Konvomep, if the Applicant should pursue an NDA resubmission with only the indications for the 40-mg omeprazole dose included; however, the acceptability of proposed labeling would be a review issue.

Type C Written Response Only, Office of Product Quality (OPQ) Meeting: November 5, 2021

- The Applicant and OPQ discussed the use of alternate analytical method (United States Pharmacopeia [USP] <301> Acid Neutralization Capacity method in place of (b) (4) for the determination of the assay of sodium bicarbonate and

[redacted]

- The Agency stated no additional NG/OG studies are necessary.

Applicant's NDA Resubmission: March 4, 2022

- In the NDA resubmission, the Applicant submitted data from Study 5032423 [redacted]

Discipline Review Letter: June 28, 2022

- The Agency sent a DR letter to the Applicant regarding [redacted]

Informal Teleconference Meeting: July 8, 2022

- The Applicant requested an informal teleconference with the Agency regarding the DR letter.
- The Applicant acknowledged that there is no information to support [redacted] however, they would submit an official response to address the DR letter.
- The Applicant inquired if it would be possible to submit labeling with [redacted] the 40-mg/1680-mg dosage (and indications) included. The Agency stated that this would be acceptable, as no concerns with the 40-mg/1680-mg dose had been identified.

Amendment Correspondence: July 15, 2022

[redacted]

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Study site(s) were not investigated in the review of this NDA. See review dated January 28, 2021.

4.2. Product Quality

In the previous review cycle, this NDA was issued a Complete Response (CR) due to inadequate control strategy for assuring the identity, strength, purity, and quality of the drug product as required by 21 CFR 314.50.

In this NDA resubmission, the Applicant has adequately addressed all the deficiencies noted in the CR letter dated January 28, 2021, as described below:

> Revise the specifications for the diluent and the constituted oral suspension to include the tests, analytical procedures, and acceptance criteria for the identification and assay of the active ingredient (API) sodium bicarbonate. Update Diluent section 3.2.P.5.1 and Kit (Constituted Suspension) section 3.2.P.5.1 accordingly.

The Applicant implemented new identification and assay methods for the sodium bicarbonate active pharmaceutical ingredient (API). The Applicant modified the specifications for the diluent and reconstituted suspension in the resubmission using a new assay method (USP <301> Acid Neutralizing Capacity titration method) and added identification test for sodium bicarbonate to assure the specificity of the assay method. The acceptance criterion of the sodium bicarbonate was not changed. The modified specifications are acceptable.

> Provide evidence that analytical procedure (b) (4) is suitable for the intended use by demonstrating that the range of recoveries does not significantly overestimate or underestimate the bicarbonate measurement. Alternatively, revise the method to minimize the wide range in percent recovery.

The Applicant proposed a new assay method of Acid Neutralizing Capacity (noted above) which addressed the deficiency noted with the previously proposed assay method (b) (4)

> Provide method validation reports for omeprazole assay procedures (b) (4) and MET-CDM-000025, and provide evidence of the comparability of the results obtained using each test.

The Applicant resolved the discrepancy between the assay and content uniformity methods for the API omeprazole by noting that the test method (b) (4) was incorrect. The correct method used in testing was CF-TM0447. Method CF-TM0447 was updated to include

omeprazole content uniformity within a bottle. Therefore, the method was not changed, and the validation submitted in the initial NDA was completed on the correct method.

> Submit batch release data and a minimum of 6 months of long-term and accelerated stability data from at least one batch of each filling configuration (90 mL, 150 mL and 300 mL) of the diluent and the constituted suspension. Testing should be performed per the revised specifications that include the identification and assay of sodium bicarbonate. The drug product batches should be packaged in the to-be-marketed container closure systems and manufactured at no less than 1/10th of the intended commercial scale. Submit in-use stability data for suspensions prepared from each of these stability batches.

The Applicant prepared new diluent batches and provided stability data (9 months in the refrigerator and 6 months at controlled room temperature) for the newly manufactured diluent and the reconstituted suspension using the revised test methods as requested by the Agency. The Applicant also updated the 24-month stability results for the registration drug product batches. Based on the stability data, the proposed 24-months expiration dating period can be granted for the drug product from the date of manufacture of either the omeprazole, USP powder component or the strawberry-flavored diluent, whichever is earlier, when stored under refrigerated conditions, 2 to 8°C (36 to 46°F). The reconstituted suspension can be stored up to 30 days under refrigerated condition.

> The above-mentioned diluent batches should be manufactured per the manufacturing process and the revised control strategy including (b) (4) . Submit representative batch record in 3.2.R and update the corresponding sections of 3.2.P.3.3 if there is any change made (See Item #6 below).

The Applicant instituted a new sodium bicarbonate assay, revised the control strategy (b) (4) and submitted new batch records. Section 3.2.P.3.3 was updated. These changes are acceptable.

> To address Deficiency #3, provide the sampling plan (sampling number and the locations) and the acceptance criteria supported by batch data and in line with the acceptance criteria at the product release. Update 3.3.P.3.4 accordingly and include the in-process testing results.

The Applicant updated the requested information and satisfactorily addressed deficiency #3 (see above).

In addition to the Product Quality deficiencies noted above, the following clinical deficiency was also addressed:

> The information provided in this NDA and reviewed amendments is not adequate to support the proposed indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients." Data to support administration of omeprazole and sodium bicarbonate for oral suspension via nasogastric and orogastric tube is necessary to support this indication.

The Applicant conducted in vitro compatibility studies for nasogastric/orogastric (NG/OG) tubes to assure the tubes are compatible with administration of the reconstituted Konvomep suspension. All sizes of the tubes were compatible with the suspension. In addition, pH, assays of omeprazole and sodium bicarbonate, and recovery of the drug product were mostly consistent before and after the suspension being pushed through the tubes. (b) (4) [redacted]

Based on the study, administration of Konvomep suspension was deemed to be acceptable for NG/OG tube sizes larger than 8 French (this size is typically used in infants). Since adult patients who require NG/OG tubes typically use much larger sizes (e.g., 16 to 18 French and above), Konvomep suspension is appropriate for administration in adult patients for the indication of reduction of risk of upper gastrointestinal bleeding, as well as the other indication(s) recommended for approval.

Based on the evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate CMC information to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

Thus, the OPQ recommends approval of NDA 213593/Original-1 for Konvomep (omeprazole and sodium bicarbonate for oral suspension), 40 mg/1680 mg (b) (4) [redacted]

(b) (4) [redacted]

The complete Integrated Quality Assessment review, dated August 22, 2022, is archived in DARRTS.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies have been conducted with Konvomep (omeprazole and sodium bicarbonate for oral suspension), 40 mg/1680 mg by the Applicant. The Applicant is relying upon FDA's findings of safety for Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 20 mg/1680 mg and 40 mg/1680 mg (NDA 021636) and Prilosec (omeprazole) delayed-release capsules, 40 mg (NDA 019810) to support the nonclinical safety of omeprazole and sodium bicarbonate for oral suspension. Based on the scientific bridge provided, the Applicant has established reliance to the nonclinical safety finding for the Zegerid 40-mg/1680-mg dose (NDA 213593/Original-1). However, clinical concerns with the higher C_{max} exposure relative to Zegerid preclude reliance upon the nonclinical safety findings for Zegerid, 20 mg/1680 mg (NDA 213593/Original-2). As noted above, Prilosec is not needed as a listed drug (LD), as all the relevant information can be supported by Zegerid for oral suspension (NDA 021636).

For the current review cycle, the Applicant has submitted additional information regarding the product formulation, justification of excipients, information on impurities, and an updated literature search spanning November 1, 2020, through December 1, 2021. No safety concerns were identified as a result of the literature search.

5.2. Referenced NDAs, BLAs, DMFs

This 505(b)(2) NDA application relies upon FDA's previous findings of safety and effectiveness for the LD, Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 40 mg/1680 mg (NDA 021636).

5.3. Pharmacology

No pharmacology studies of omeprazole and sodium bicarbonate for oral suspension, 40 mg/1680 mg were submitted by the Applicant. Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it 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 Applicant submitted a published central nervous system safety pharmacology study. The aims of this study by Ali and colleagues were to determine whether repeated administration of omeprazole produces anxiety and impairs memory, and if so, whether these changes were associated with changes in brain serotonin and dopamine metabolism, and serotonin 1A (5-HT

1A) receptor expression in the raphe and hippocampus (Ali et al. 2021). Albino Wistar rats were treated intraperitoneally with 10 or 20 mg/kg/day of omeprazole for 15 days (water-for-injection was used as a control) and subjected to various neurobehavioral assessments on Days 1, 7, and 15. Rats treated with omeprazole had decreased motor activity and performance in the open field activity and elevated plus maze, which are measures of anxiety-like behavior; and decreased learning acquisition and memory retention in the Morris water maze and probe test. Serotonin and serotonin metabolite levels were significantly decreased in omeprazole-treated rats, but there was no significant difference in dopamine or dopamine metabolism as compared to control. Serotonin receptor expression was also decreased in the raphe region and hippocampus as compared to control. The authors concluded that long-term use of omeprazole could produce anxiety, reduce motor activity, and impair cognition.

5.4. ADME/PK

No pharmacokinetic studies were conducted by the Applicant, however, a published study by Dujic and colleagues was submitted (Dujic et al. 2021). The aim of this study was to explore the interaction between omeprazole and the antidiabetic drug gliclazide, which are both metabolized by CYP2C19. A physiologically based pharmacokinetic (PK) modeling simulation predicted a 1.4 to 1.6-fold higher gliclazide AUC after 5-day treatment with 20 mg omeprazole in all CYP2C19 phenotype groups except in poor metabolizers. The predicted gliclazide AUC increased 2.1- and 2.5-fold in intermediate metabolizers and 2.6- and 3.8- fold in normal/rapid/ultrarapid metabolizers group after simulated 20-day dosing with 40 mg omeprazole once and twice daily, respectively. These predicted results were corroborated by findings in patients with type 2 diabetes, which demonstrated 3.3-fold higher odds of severe gliclazide-induced hypoglycemia in normal/rapid/ultrarapid metabolizers concomitantly treated with omeprazole. These results indicate omeprazole may increase exposure to gliclazide and increase risk of gliclazide-associated hypoglycemia.

5.5. Toxicology

5.5.1. General Toxicology

No general toxicology studies have been submitted. The Applicant is relying on FDA's findings of safety for the LD, Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 40 mg/1680 mg to support the nonclinical safety of omeprazole and sodium bicarbonate for oral suspension, 40 mg/1680 mg.

5.5.2. Genetic Toxicology

No genotoxicity studies were submitted by the Applicant. Omeprazole was positive for clastogenic effects in an in vitro human lymphocyte chromosomal aberration assay, in one of two in vivo mouse micronucleus tests, and in an in vivo bone marrow cell chromosomal aberration assay. Omeprazole was negative in the in vitro Ames test, an in vitro mouse lymphoma cell forward mutation assay and an in vivo rat liver DNA damage assay.

The Applicant submitted a published study by Braga and colleagues (Braga et al. 2021). In this study, Swiss mice were treated with 10, 20, and 40 mg/kg omeprazole with or without antioxidants retinol palmitate (100 IU/kg) and ascorbic acid (2.0µM/kg) for 14 days. Stomach cells, bone marrow, and peripheral blood lymphocytes were submitted to comet assay and micronucleus test. The results suggested that omeprazole induced genotoxicity and mutagenicity in the treated cells, however the effects were modulated and/or inhibited when omeprazole was combined with antioxidants.

5.5.3. Carcinogenicity

In a 24-month carcinogenicity study in rats, a dose-related significant increase in gastric carcinoid tumors and enterochromaffin-like cell hyperplasia was observed in both male and female animals. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other PPIs or high doses of H2-receptor antagonists.

5.5.4. Reproductive and Developmental Toxicology

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at doses up to 69.1 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) during organogenesis did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis) administered during organogenesis produced dose-related increases in embryolethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138 mg/kg/day (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis), administered prior to mating through the lactation period.

5.5.5. Other Toxicology Studies

Safety Assessment of Excipients

There are no safety concerns for the levels of the excipients present in omeprazole and sodium bicarbonate for oral suspension, 40 mg/1680 mg. The proposed formulation contains compendial excipients with well-established safety levels in the Inactive Ingredients Database.

The only noncompendial ingredient not listed in the Inactive Ingredients Database is the strawberry flavoring. (b) (4) The Applicant provided a Letter of Authorization to cross-reference this DMF. Although the ingredients in the flavoring are proprietary, they are either approved by the Agency and/or appear in a reliable published industry list for use in foods for human consumption. All flavoring ingredients in the (b) (4) are considered generally recognized as safe.

(b) (4)
(b) (4) propylene glycol and glycerin, which are in the Inactive Ingredients Database with maximum daily exposure levels of 27,120 mg and 28,208 mg, respectively, for an oral suspension. The strawberry flavoring can be safely used at levels up to 4.0% (w/w, approximately 1.1% w/v). The constituted Omeprazole Suspension formulation only contains (b) (4) (w/v) of strawberry flavoring and is therefore safe to use.

Safety Assessment of Impurities

The drug substance, omeprazole USP, contains organic impurities that have been characterized and reported in the drug substance manufacturer's DMF. There are no safety concerns with the process impurities, which include 2-Mercapto-5-methoxy benzimidazole, omeprazole N-oxide, omeprazole sulphone, desmethoxy omeprazole, (b) (4) omeprazole sulfone N-oxide, and omeprazole 4-chloro analog.

Residual solvents have been identified and are controlled in accordance with USP <467> and tested in accordance with USP <232>. These potential residual solvents are (b) (4) An elemental impurities risk assessment was conducted, and the results were provided in the DMF. No elemental impurities were detected in three consecutive batches assessed and omeprazole drug substance was determined to comply with International Council for Harmonisation draft guidance for industry *Q3D(R2) Guideline for Elemental Impurities* (May 2021).

The drug substance, sodium bicarbonate USP, is present in the strawberry-flavored diluent. It is tested according to the current USP monograph. The only potential source of organic impurities is the minimal amount remaining of low organic (b) (4) used as a starting material. Organic impurities in (b) (4) are below the USP monograph limit of (b) (4) ppm and do not exceed the minimum threshold for Reporting, Identification, or Qualification per Guidance for Industry Q3A. Residual solvents are not found as no solvents are used in the manufacturing and handling.

6. Clinical Pharmacology

6.1. Executive Summary

In this resubmission, the Applicant has proposed to address the deficiencies listed in the CR letter dated January 28, 2021. Upon the review of the initial NDA submission, the Agency concluded that the comparable bioavailability between Konvomep (omeprazole and sodium bicarbonate for oral suspension), 40 mg/1680 mg and Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 40 mg/1680 mg was demonstrated for both C_{max} and AUC (meeting the bioequivalence criteria), and a scientific bridge between Konvomep, 40 mg/1680

mg and Zegerid, 40 mg/1680 mg was established. Although no clinical pharmacology deficiencies for Konvomep, 40 mg/1680 mg were identified, OPQ deficiencies precluded its approval under the initial NDA.

[redacted]

In this resubmission, the Applicant has conducted [redacted] (Study 5032423) [redacted]

The Applicant proposed to support the safety [redacted] the Applicant's proposed reliance upon the safety of [redacted] is not acceptable.

[redacted] provided by the Applicant was insufficient to support [redacted] Therefore, the Applicant did not demonstrate that reliance upon the FDA's findings of safety for the [redacted] was scientifically appropriate. Refer to Section 8.2.5 for additional details.

Recommendations

NDA 213593/Original-1

The clinical pharmacology data submitted in the initial NDA submission were adequate to recommend approval of the Konvomep, 40-mg/1680-mg dose for indications specific to the 40 mg dose of omeprazole.

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6.2.1. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosage for treatment of benign gastric ulcer and reduction of risk of upper GI bleeding in critically ill patients is consistent with the listed drug and acceptable.

The Applicant originally sought (b) (4)
able 6 summarizes the dosing regimens initially proposed by the Applicant for each of the indications.

Table 6. Proposed Dosage Regimens for Konvomep (Omeprazole and Sodium Bicarbonate for Oral Suspension) by Indication for Adults 18 Years and Older

Indication	Recommended Dosage	Treatment Duration
[redacted]		
Treatment of benign gastric ulcer	40 mg (20 mL) once daily	4 to 8 weeks
[redacted]		
Reduction of risk of upper GI bleeding in critically ill patients	40 mg (20 mL) initially; followed by 40 mg 6 to 8 hours later; and 40 mg once daily thereafter	14 days

Source: Reviewer created table adapted from proposed PI submitted with NDA 213593 on March 4, 2022
Abbreviations: EE, erosive esophagitis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NDA, new drug application

[redacted] treatment of adults for benign gastric ulcer, and reduction of risk of upper GI bleeding in critically ill patients (Table 7).

Table 7. Dosage Regimens of Konvomep (Omeprazole and Sodium Bicarbonate for Oral Suspension) by Indication for Adults 18 Years and Older

Indication	Recommended Dosage	Treatment Duration
Treatment of benign gastric ulcer	40 mg (20 mL) once daily	4 to 8 weeks
Reduction of risk of upper GI bleeding in critically ill patients	40 mg (20 mL) initially; followed by 40 mg 6 to 8 hours later; and 40 mg once daily thereafter	14 days

Source: Reviewer created table adapted from proposed PI submitted with NDA 213593 on March 4, 2022
Abbreviations: EE, erosive esophagitis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NDA, new drug application

Therapeutic Individualization

The Applicant has not proposed any therapeutic individualization for their product in the PI based on intrinsic/extrinsic factors. This is consistent with the approved labeling language for the LD Zegerid.

Outstanding Issues

[redacted]

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The NDA did not contain data from clinical safety or efficacy trials. The application relies upon the findings of safety and effectiveness for the LD, Zegerid (omeprazole and sodium bicarbonate) for oral suspension (NDA 021636).

Two relative BA studies were submitted in support of a scientific bridge between Konvomep and the LD, Zegerid, see Table 8 below.

Table 8. Table of Relative Bioavailability Studies Submitted in Support of a Scientific Bridge to Zegerid for Oral Suspension

Description	Study OME-RM02-001[1] (N=60 Healthy Subjects)	Study 5032423[2] (b) (4)
Trial design	Open-label, single dose, randomized, three-treatment, three-period, triple crossover at a single U.S. site	
Treatment arms	Treatment A: Konvomep, 40 mg/1680 mg Treatment B: Zegerid for oral suspension, 40 mg/1680 mg Treatment C: Omeprazole DR capsules, 40 mg (7-day washout period between treatment arms)	
Endpoints	Primary PK endpoints: C_{max}, AUC_{0-t}, and AUC_{0-inf} Secondary PK endpoints: T_{max}, apparent volume of distribution (Vz/F), apparent clearance (CL/F), terminal elimination rate constant (K_{el}), and elimination half-life ($t_{½}$) Secondary safety endpoint: safety and tolerability	

Source: Reviewer Table.
[1] Refer to the unireview for the initial submission of NDA 213593, dated January 28, 2021, for the clinical review of this study.
[2] Study 5032423 is reviewed within this unireview.
Abbreviations: AUC_{0-inf}, area under the plasma concentration versus time curve extrapolated to infinity; AUC_{0-t}, area under the plasma concentration to the last measurable concentration; C_{max}, maximum plasma concentration; DR, delayed-release; NDA, new drug application; PK, pharmacokinetic; T_{max}, time to peak drug concentration; U.S., United States.

7.2. Review Strategy

The Applicant is proposing to rely upon the FDA's findings of safety and effectiveness for the listed drug, Zegerid (omeprazole and sodium bicarbonate) for oral suspension (NDA 021636). As noted above, no clinical safety or efficacy trials were conducted to support this NDA. The review focused on the two relative BA studies (i.e., Study OME-RM02-001 and Study 5032423), additional information submitted by the Applicant to support the proposed reliance on the

FDA's findings of safety, for the LD, and the safety of PPIs from the scientific literature and postmarketing data.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

No clinical efficacy trials were conducted to support this NDA. The Applicant is proposing to rely upon the FDA's findings of safety and effectiveness for the LD, Zegerid (omeprazole and sodium bicarbonate) for oral suspension; NDA 021636. See Section 6 for the relative BA studies that supported the scientific bridge to the LD.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review of the NDA resubmission focuses primarily on the Agency's previous findings of safety (and effectiveness) for Zegerid (omeprazole and sodium bicarbonate) for oral suspension (NDA 021636), the safety results from the relative BA studies (OME-RM02-001 and 5032423) conducted in healthy adult subjects, additional information submitted by the Applicant to support the proposed reliance on the FDA's findings of safety for the LD, and the safety of PPIs as available from the scientific literature and postmarketing data.

Safety data from Study 5032423 are described below in Section 8.2.4. As noted in the unireview dated January 28, 2021, no safety concerns were identified during the review of Study OME-RM02-001 in the initial NDA submission.

Additionally, the Agency continues to evaluate emerging safety signals for the proton pump inhibitor (PPI) class (e.g., omeprazole), including adverse reactions that have been reported in patients with long-term PPI exposure from chronic treatment with PPIs. These safety concerns have resulted in multiple class-wide SLCs for PPIs.[1] Refer to Section 8.2.5 for a discussion of safety concerns related to PPI exposure.

[1] Under section 505(o)(4) of the Food, Drug, and Cosmetic Act (FDCA)

8.2.2. Review of the Safety Database

Overall Exposure

(b) (4)

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

(b) (4)

Compliance With Good Clinical Practices

The Applicant attested that the study was conducted in compliance with Good Clinical Practice.

Financial Disclosure

No reportable financial conflicts of interest between the Applicant and the investigator involved in the conduct of this study.

Patient Disposition

(b) (4)

Protocol Violations/Deviations

(b) (4)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All doses of study drug were administered by study site personnel and mouth check was performed to confirm oral dosing. The date and time that study drug was administered to each subject were recorded.

(b) (4)

Safety Parameters and Categorization of Adverse Events

The safety parameters included adverse events (AEs), clinical laboratory parameters, physical exam findings, electrocardiogram, and vital signs. An AE that occurred during the study period was considered a treatment-emergent adverse event. All subjects who received at least one dose of study drug were included in the safety analysis.

8.2.4. Safety Results

(b) (4)

8.2.5. Analysis of Submission-Specific Safety Issues

Based on the Study 5032423 (b) (4)
(b) (4)

Study 5032423 did not adequately support the scientific appropriateness of the Applicant's proposed reliance upon the FDA's findings of safety for the LD, Zegerid.

(b) (4)
the 40-mg/1680-mg dose of Zegerid is approved treatment of benign gastric ulcer for 4 to 8 weeks and reduction of risk of upper GI bleeding for up to 14 days. These indications are for short-term use, and the benefit-risk for these indications and patient populations may be different, especially in the population at risk for

upper GI bleeding. (b) (4)

(b) (4)

(b) (4)

(b) (4) The Agency continues to evaluate emerging safety signals for the PPI drug class. Per FDA review of postmarketing pharmacovigilance reports and large, observational epidemiological studies, select serious or otherwise clinically significant adverse reactions have been determined to be associated with higher PPI doses and/or longer durations of use. These adverse reactions have been characterized in the Warning and Precautions sections of PPI labels and via FDA Amendments Act SLCs. In brief, as adapted from the LD Zegerid PI, selected adverse reactions include (Salix 2022):

- *Bone Fracture:* Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as

multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

- *Clostridium difficile-Associated Diarrhea:* Published observational studies suggest that PPI therapy may be associated with an increased risk of *Clostridium difficile*-associated diarrhea, especially in hospitalized patients. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
- *Cyanocobalamin (Vitamin B-12) Deficiency:* Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo - or achlorhydria.
- *Hypomagnesemia and Mineral Metabolism:* Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy.
- *Fundic Gland Polyps:* PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Use the shortest duration of PPI therapy appropriate to the condition being treated.

In addition, the scientific community acknowledges that long-term use of PPIs carries the risk of potential adverse reactions, including the labeled risk of fractures, *Clostridium difficile* diarrhea, hypomagnesemia, and vitamin B12 deficiency. Many recent publications acknowledge that substantial numbers of patients are receiving PPIs off-label and/or unnecessarily for conditions or symptoms for which they would not have been expected to provide benefit. Furthermore, many patients who are on PPI treatment for appropriate indications are receiving excessively high daily doses (Vaezi et al. 2017). Clinical recommendations from peer-reviewed, published literature conclude, “the best strategy is to prescribe PPIs at the lowest dose on a short-term basis when appropriately indicated so that the potential benefits outweigh any adverse effects” (Nehra et al. 2018). In addition, the American College of Gastroenterology recently published a clinical practice update on “de-prescribing” of PPIs in an effort to reduce safety risks, among other concerns (Targownik et al. 2022).

The review team recognizes that there is an absence of data to establish whether safety risks associated with PPIs are associated with increases in C_{max} versus AUC versus both C_{max} and AUC.

(b) (4) (b) (4)

(b) (4)

(b) (4)

[redacted]

8.2.6. Safety in the Postmarket Setting

PPI-Related Safety Label Changes Identified Through Postmarketing Experience

Data from postmarketing use of PPIs have resulted in multiple class safety labeling updates since the approval of Zegerid (omeprazole and sodium bicarbonate) for oral suspension in 2004. See Section 8.2.5 above.

There are other, potential postmarketing safety issues related to cardiac disorders, pneumonia, and erectile dysfunction, that are currently under investigation by the Agency but there are no pending SLCs at this time.

8.3. Statistical Issues

N/A- no statistical issues were identified during review of this application.

8.4. Conclusions and Recommendations

The following are the conclusions and recommendation for each dose of Konvomep, and associated indications, based on the benefit and risks assessed for each dose, respectively.

NDA 213593/Original-1

A scientific bridge has been established between Konvomep (omeprazole and sodium bicarbonate for oral suspension), 40 mg/1680 mg and the LD Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 40 mg/1680 mg based on Study OME-RM02-001, as reviewed in the initial NDA submission. This bridge is adequate to justify the Applicant's proposed reliance upon FDA's findings for the safety and effectiveness for Zegerid for oral suspension for the relevant indications in adults: treatment of benign gastric ulcer and reduction of risk of upper GI bleeding.

The overall benefit-risk is favorable for Konvomep, 40 mg/1680 mg. No new safety signals were identified. The review team recommends the approval of Konvomep, 40 mg/1680 mg, for the relevant indications. The identified risks of the PPIs can be mitigated through labeling and routine pharmacovigilance is recommended. No additional risk management strategies are recommended at this time.

(b) (4)

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee was not held, and no external consultants were involved during the review of this NDA application.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U. S. C. 335), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Konvomep (omeprazole and sodium bicarbonate for oral suspension) is a fixed dose combination containing omeprazole and sodium bicarbonate. However, this product is not a

novel fixed dose combination. The Applicant has proposed (b) (4)

(b) (4) dose contains 40 mg omeprazole and 1,680 mg sodium bicarbonate per (b) (4) and is being developed in adults for the treatment of active benign gastric ulcer and the reduction of risk of upper GI bleeding in critically ill patients. These indications are already approved in adults at the same dosage strength for Zegerid (omeprazole and sodium bicarbonate) for oral suspension, 40 mg /1680 mg.

NDA 213593/Original-1

The 40 mg/1680 mg dosage strength of Konvomep does not represent a new dosage form, dosing regimen, route of administration, or indication for this combination of active ingredients not already FDA approved for Zegerid for oral suspension. Therefore, this application is not subject to PREA requirements.

(b) (4)

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant's proposed labeling was reviewed, and recommended revisions and comments have been communicated to the Applicant during the review of this NDA.

The following is a summary based upon the PI submitted on July 18, 2022.

NDA 213593/Original-1

The prescribing information includes similar information to found in the Zegerid PI, approved March 4, 2022, with the exception of the following (Salix 2022).

HIGHLIGHTS, Product Title

The proprietary name Konvomep was found to be conditionally acceptable by the Office of Medication Error Prevention and Risk Management on June 6, 2022.

INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION

Only the indications and dosage regimens that utilize the 40-mg/1680-mg dose are included:

- Short-term treatment (4 to 8 weeks) of active benign gastric ulcer in adults.
- Reduction of risk of upper GI bleeding in critically ill adult patients.

Preparation and administration instructions for Konvomep by both oral route and via NG/OG tube are provided including:

- Konvomep is a kit comprised of two bottles (one of omeprazole powder and one of sodium bicarbonate diluent) and is for reconstitution by a healthcare provider for use in adults

- The diluent is added to the bottle containing omeprazole powder and must be shaken prior to dispensing and prior to each use by the patient/caregiver.
- The reconstituted suspension should be stored under refrigerated conditions for up to 30 days.
- Enteral feeding should be suspended approximately 3 hours before and 1 hour after NG/OG administration.

DOSAGE FORMS AND STRENGTHS, DESCRIPTION, STORAGE AND HANDLING

The description of the product is as follows:

> For Oral Suspension: 2 mg omeprazole and 84 mg sodium bicarbonate per mL of a pink to red hazy, strawberry-flavored liquid after reconstitution in 90 mL, 150 mL, or 300 mL bottles. Each kit contains a bottle of omeprazole as a white to off-white powder and a strawberry-flavored diluent containing sodium bicarbonate as a slightly hazy red liquid

WARNINGS AND PRECAUTIONS

The sodium content of the product (in term of the bicarbonate salt and the total sodium content) is included to inform healthcare professionals when administering to patients on a sodium-restricted diet or those at risk for developing congestive heart failure.

> Sodium content: Each mL of reconstituted KONVOMEP contains 84 mg of sodium bicarbonate (equivalent to 1 mEq/mL of sodium). The total content of sodium, from active and inactive ingredients per mL of reconstituted KONVOMEP is 26.3 mg (1.14 mEq). Total sodium content per 40 mg dose (volume of 20 mL) of KONVOMEP is 526 mg (22.8 mEq).

DRUG INTERACTIONS

The PI for Zegerid does not recommend dosage adjustment of omeprazole when used with voriconazole for the indications in which Zegerid is approved; however, the voriconazole PI has additional information on the nature of the interaction with omeprazole, so the information was revised to include reference to the voriconazole PI for healthcare professionals who may wish to make a patient-specific determination of whether dosage adjustment of Konvomep is warranted.

> Voriconazole: Dosage adjustment of KONVOMEP is not usually required. See full prescribing information for voriconazole

USE IN SPECIFIC POPULATIONS

Konvomep is not being labeled (b) (4)

(b) (4)

(b) (4) The PK results of the increased exposure in these populations will remain in Section 12.3.

CLINICAL PHARMACOLOGY, Pharmacokinetics

The PK data was revised to include results obtained with Konvomep on day 1. Unlike Zegerid, there are no PK available on day 7. Therefore, a general statement about the expected increase in exposure following repeated doses due to autoinhibition of CYP2C19 was included:

> Omeprazole is a time-dependent autoinhibitor of CYP2C19. The bioavailability of omeprazole from omeprazole and sodium bicarbonate for oral suspension increases upon repeated administration.
>
> Following repeated once-daily dosing of omeprazole at a dose of 40 mg with sodium bicarbonate, a higher omeprazole mean C_{max} (1.4-fold on Day 7) and increased AUC(2-fold on Day 7) were observed. The increase in mean steady-state AUC (on Day 7) for omeprazole at a dose of 40 mg was greater than dose proportional relative to a lower dose.

CLINICAL STUDIES

The description of the studies and tables of results for the benign gastric ulcer indication have been modified (b) (4)

(b) (4)

12. Risk Evaluation and Mitigation Strategies (REMS)

No risk revaluation and mitigation strategies are recommended.

13. Postmarketing Requirements and Commitments

None.

14. Office Director (or Designated Signatory Authority) Comments

I concur with the recommendation of the review team to issue an Approval Letter for Konvomep (omeprazole and sodium bicarbonate for oral suspension) NDA 213593/Original-1 (b) (4) This is a 505(b)(2) application that relies upon FDA's previous findings of safety and effectiveness for the listed drug (LD), Zegerid (omeprazole and sodium bicarbonate) for oral suspension (NDA 021636).

The proposed product is available in one strength and contains 2 mg omeprazole and 84 mg sodium bicarbonate per mL. It is to be constituted to an oral suspension by a healthcare provider before dispensing to the patient. The proposed indications and dosing regimens are (b) (4) 40 mg of the omeprazole component. (b) (4)

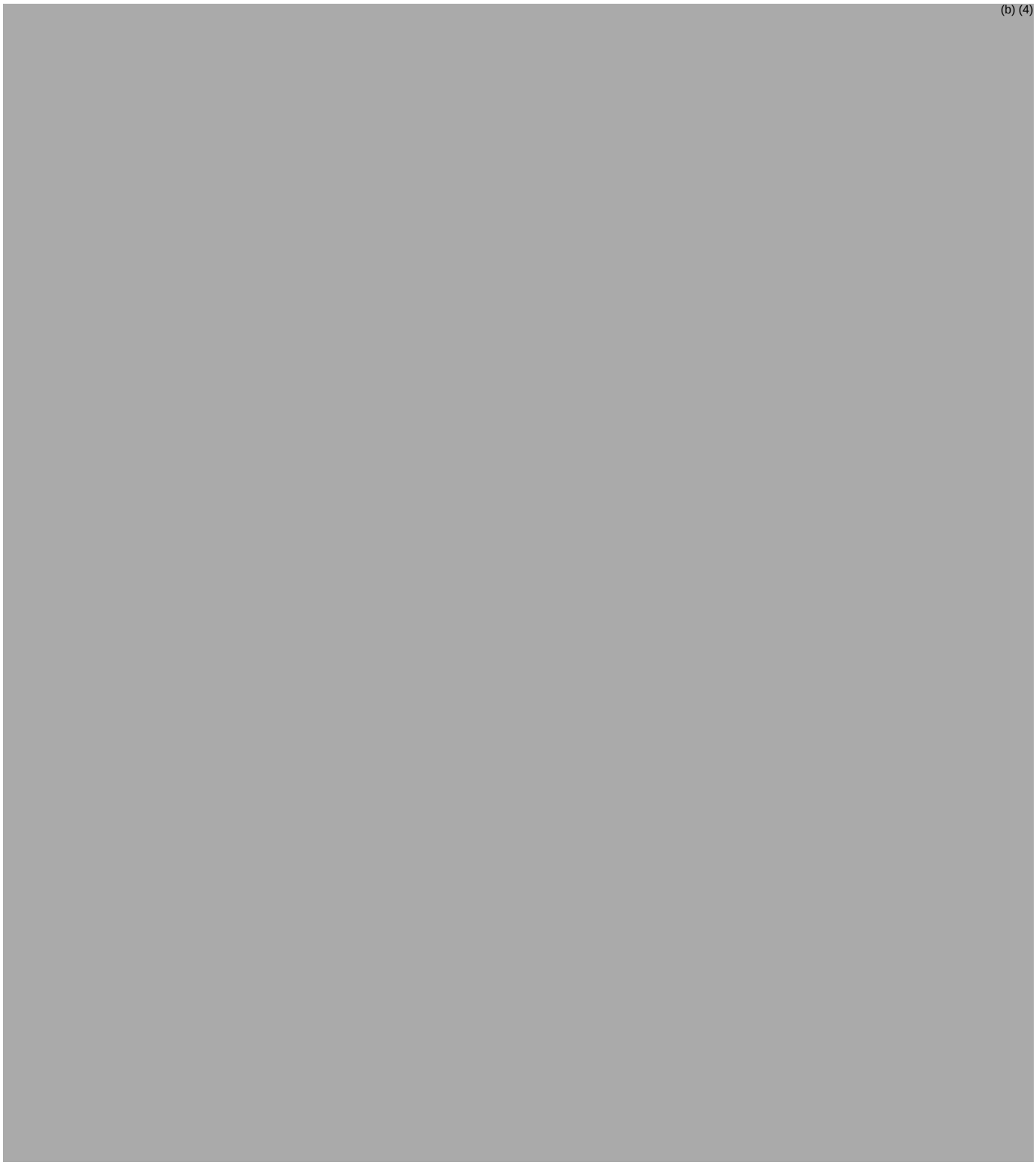
NDA 213593/Original-1

I agree with the review team that the Applicant has adequately established a scientific bridge between the proposed product and Zegerid at the dose of 40 mg (both containing 40 mg omeprazole and 1680 mg sodium bicarbonate) through the relative BA study included in the initial submission of the NDA (Study OME-RM02-001) to justify the proposed reliance upon the previous findings of safety and effectiveness for the LD. Additionally, the product quality issues that led to the issuance of a CR for the initial NDA have been satisfactorily resolved.

The 40-mg/1680-mg dose of Konvomep does not represent a new dosage form, dosing regimen, route of administration, or indication for this combination of active ingredients that was previous approved for Zegerid for oral suspension under NDA 021636. Therefore, NDA 213593/Original-1 is not subject to PREA requirements, and no postmarketing requirements or commitments will be issued with the Approval Letter.

The Agency continues to evaluate emerging safety signals for the proton pump inhibitor (PPI) class (e.g., omeprazole), including adverse reactions that have been reported in patients with long-term PPI exposure from chronic treatment with PPIs. These safety concerns have resulted in multiple class-wide Safety Labeling Changes (SLCs) for PPIs. No new safety signals were identified during review of the data submitted in support of the application; however, as a PPI, identified class safety concerns are applicable and should be included in the PI for Konvomep, 40 mg/1680 mg.

(b) (4)



15. Appendices

15.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): 1

Was a list of clinical investigators provided:	Yes	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.2. OCP Appendices (Technical Documents Supporting OCP Recommendations)

The Applicant conducted two relative bioavailability (BA) studies for the omeprazole oral suspension clinical development program (Study OME-RM02-001 and Study 5032423).

Study OME-RM02-001 was previously reviewed and found acceptable during the review of initial NDA. Briefly, Study OME-RM02-001 showed that the omeprazole bioavailability after administration of Konvomep, 40 mg/840 mg (Treatment A) was comparable to Zegerid for oral suspension (Treatment B) under fasting conditions. The 90% CI for the ratio of the geometric means of AUC_{0-t}, AUC_{inf} and C_{max} were within the bioequivalence acceptance criteria of 80-125%. Refer to the Unireview of NDA 213593 dated January 28, 2021, for details regarding Study OME-RM02-001.

Study 5032423 (b) (4)
(b) (4)

Table 9. Study Information, Study 5032423

(b) (4)

(b) (4) study 5032423.

(b) (4)

Study 5032423 (b) (4)

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/s/

JOETTE M MEYER
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ERICA M LYONS
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NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA - 505(b)(2)
Application Number	213593
Priority or Standard	Standard
Submit Date	Mar 30, 2020
Received Date	Mar 30, 2020
PDUFA Goal Date	Jan 30, 2021
Division/Office	OND/ OII / DG
Review Completion Date	Jan 28, 2021
Established/Proper Name	Omeprazole and Sodium Bicarbonate for Oral Suspension
(Proposed) Trade Name	Konvomep
Pharmacologic Class	Proton Pump Inhibitor (PPI)
Applicant	Azurity Pharmaceuticals, Inc.
Dosage form	For Oral Suspension: 2 mg omeprazole and 84 mg sodium bicarbonate per mL after reconstitution in 90 mL, 150 mL, or 300 mL bottles
Applicant proposed Dosing Regimen	(b) (4)
Applicant Proposed Indication(s)/Population(s)	(b) (4) 2) Short-term treatment of active benign gastric ulcer for 4 to 8 weeks (b) (4) 6) Reduction of risk of upper GI bleeding in critically ill adult patients for 14 days
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	(b) (4) Gastric Ulcer (b) (4) Gastrointestinal Hemorrhage
Recommendation on Regulatory Action	Complete Response

Recommended Indication(s)/Population(s) (if applicable)	Nonapplicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Nonapplicable
Recommended Dosing Regimen	Nonapplicable

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Reviewers of Multi-Disciplinary Review and Evaluation

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ATL, Application Technical Lead; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; DPV, Division of Pharmacovigilance; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; RBPM, Regulatory Business Project Manager; RPM, Regulatory Project Manager; TL, Team Leader

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
API	active pharmaceutical ingredient
BA	bioavailability
BE	bioequivalence
BLA	biologics license application
CFR	Code of Federal Regulations
DR	delayed-release
EE	erosive esophagitis
ECG	electrocardiogram
FDA	Food and Drug Administration
GERD	gastroesophageal reflux disease
IID	Inactive Ingredients Database
IND	investigational new drug
IQA	Integrated Quality Assessment
IR	immediate release
LC	label claim
LD	listed drug
NDA	new drug application
PI	prescribing information
PK	pharmacokinetics
PP	polypropylene
PPI	proton pump inhibitor
PREA	Pediatric Research Equity Act
PUD	peptic ulcer disease
REMS	risk evaluation and mitigation strategy
TEAE	treatment-emergent adverse event
USP	United States Pharmacopeia

1 Executive Summary

1.1. Product Introduction

Proposed trade name: Konvomep

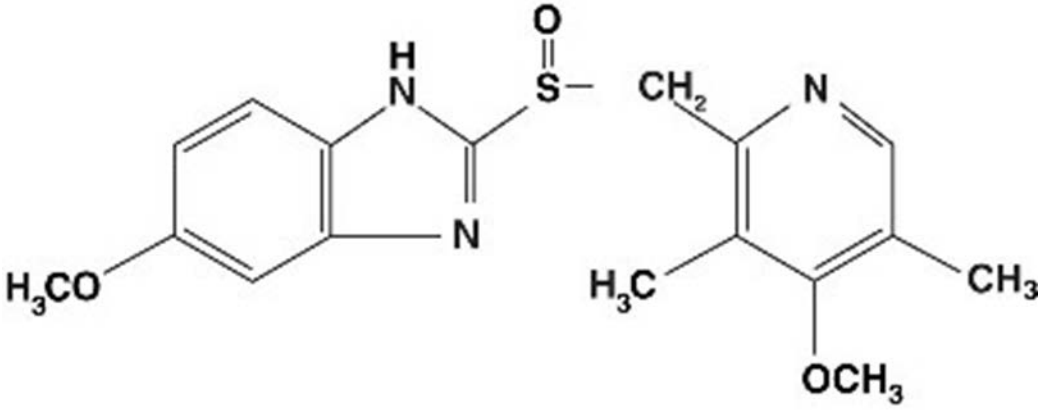
Generic name: RM-02 Kit (omeprazole and sodium bicarbonate for oral suspension)

Chemical name: 5-methoxy-2- [[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole

Empirical formula: C17H19N3O3S

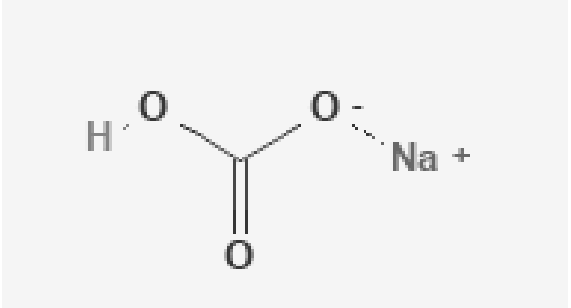
Molecular weight: 345.42

Figure 1. Structural Formula Omeprazole



Source: (Drugs@FDA: FDA-Approved Drugs)

Figure 2. Structural Formula Sodium Bicarbonate



Source: (National Center for Biotechnology Information, 2021)

Drug class: Gastric parietal cell H+/K+ adenosine triphosphatase (ATPase) enzyme inhibitor; also referred to as proton pump inhibitor (PPI)

Route of Administration, Description, and Formulation: Omeprazole and sodium bicarbonate for oral suspension is proposed in three package sizes (90, 150 and 300 mL). The 90-, 150- and

300-mL kits include one bottle containing omeprazole powder United States Pharmacopeia (USP) (0.18, 0.3 or 0.6 g) and one bottle containing strawberry-flavored diluent (90, 150 and 300 mL) for constitution. Omeprazole and sodium bicarbonate for oral suspension when constituted, contains the equivalent of 2 mg/mL of omeprazole and 84 mg/mL of sodium bicarbonate for oral administration; 20 mL of the constituted product provides a 40 mg oral dose of omeprazole and 1680 mg of sodium bicarbonate. (b) (4)

Omeprazole Delayed-Release (Prilosec, Omeprazole DR)

Omeprazole has been approved for use in the United States since 1989. Omeprazole suppresses gastric acid secretion by specific inhibition of the H+/K+ adenosine triphosphatase (ATPase) enzyme system at the secretory surface of the gastric parietal cell to block the final step of acid production. Like other PPIs, omeprazole is acid-labile and is rapidly degraded by gastric acid. Currently available products are manufactured with enteric-coatings in delayed-release (DR) formulations to protect the omeprazole from rapid degradation upon exposure to acid. Omeprazole is currently indicated for the short-term treatment of active duodenal ulcer, short term treatment of active benign gastric ulcer, treatment of symptomatic gastroesophageal reflux disease (GERD), treatment of erosive esophagitis (EE) due to acid-mediated GERD, maintenance of healing of EE due to acid-mediated GERD, treatment of pathological hypersecretory conditions, and *Helicobacter Pylori* (*H. pylori)* eradication (when used with clarithromycin and amoxicillin). Omeprazole is approved in children one month of age and older for the treatment of EE due to acid-mediated GERD and in children one year of age and older for the treatment of symptomatic GERD and maintenance of healing of EE due to acid-mediated GERD.

Omeprazole is currently available as 10 mg, 20 mg, and 40 mg capsules and 2.5 mg and 10 mg unit dose packets for oral suspension. It is also available over-the-counter (OTC) for the treatment of frequent heartburn as a 20mg tablet.

Omeprazole/Sodium Bicarbonate (Zegerid)

Zegerid is a combination of omeprazole immediate release (IR) and sodium bicarbonate and was approved in the United States as a powder for oral suspension in 2004 and as a capsule in 2006. In this formulation, sodium bicarbonate neutralizes gastric acid to protect omeprazole from gastric acid degradation. Although the neutralization of gastric acid is a direct pharmacologic action of the sodium bicarbonate, the effect is transient and does not contribute to the therapeutic effect of the product for chronic acid-related conditions that require continuous suppression of gastric acid for four to eight weeks or longer.

Zegerid is indicated for the short-term treatment of active duodenal ulcer, short-term treatment of active benign gastric ulcer, treatment of symptomatic GERD, short-term treatment

of EE due to acid-mediated GERD, maintenance of healing of EE due to acid-mediated GERD, and reduction of risk of upper GI bleeding in critically ill adult patients. Zegerid is not approved for use in pediatric patients.

Zegerid is available as an oral suspension in unit-dose packets of either 20 mg omeprazole and 1680 mg sodium bicarbonate or 40 mg omeprazole and 1680 mg sodium bicarbonate and as capsules of 20 mg of omeprazole and 1100 mg sodium bicarbonate or 40 mg of omeprazole and 1100 mg sodium bicarbonate. Zegerid is also available OTC as unit-dose packets of 20 mg omeprazole and 1680 mg sodium bicarbonate.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This 505(b)(2) NDA application proposes reliance on FDA's previous findings of safety and effectiveness for the listed drugs (LD), Zegerid (omeprazole/sodium bicarbonate) for oral suspension and Prilosec (omeprazole DR capsules), as supported by study OME-RM02-001, an open-label, single dose, randomized, three-treatment, three-period, triple crossover, pharmacokinetic and bioavailability (BA) study of omeprazole and sodium bicarbonate for oral suspension (Konvomep) 40 mg/1680 mg, compared to Zegerid (omeprazole/sodium bicarbonate) powder for oral suspension 40 mg/1680 mg, and Omeprazole DR 40 mg capsules in healthy adult subjects under fasted conditions. Omeprazole DR, an approved generic product and a reference listed drug in the Orange Book, was selected as an acceptable alternative for this study due to the discontinuation of Prilosec capsules.

No efficacy studies were conducted to support this NDA. The determination of efficacy is based on the Applicant's demonstration of comparable BA to the LD. Although the Applicant successfully demonstrated that the relative BA of omeprazole and sodium bicarbonate for oral suspension 40 mg/1680 mg was comparable to Zegerid 40 mg/1680 mg, (b) (4)

(b) (4)

Additionally, the Applicant did not provide sufficient data to support indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients" in this NDA and reviewed

amendments. Data to support administration of omeprazole and sodium bicarbonate for oral suspension via nasogastric and orogastric tube is needed to support this indication.

Furthermore, the submission lacks sufficient information to demonstrate that the proposed control strategy for the omeprazole and sodium bicarbonate active pharmaceutical ingredients (APIs) of this combination product meets the regulatory standard. As per the January 26, 2021 Integrated Quality Assessment (IQA) review, the proposed control strategy is insufficient to assure the identity, strength, purity, quality, and bioavailability of the drug product as required by 21 CFR 314.50. This application cannot be recommended for approval until adequate controls for the APIs, sodium bicarbonate and omeprazole, are established, and the Applicant has demonstrated that drug product with the requisite quality can be manufactured consistently. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability (21 CFR 314.125(b)(1)).

Without sufficient information to support the characterization of the APIs in the product, a determination of the effectiveness of omeprazole and sodium bicarbonate for oral suspension cannot be supported. The Division recommends a Complete Response action for the NDA.

(b) (4)

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

(b) (4)

comparable bioavailability (BA) to the listed drug (LD). Although the Applicant successfully demonstrated that the relative BA of omeprazole and sodium bicarbonate for oral suspension 40 mg/1680 mg was comparable to Zegerid 40 mg/1680 mg, (b) (4)

Additionally, the information provided in this NDA and reviewed amendments is not adequate to support the proposed indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients". Data to support administration of omeprazole and sodium bicarbonate for oral suspension via nasogastric and orogastric tube is necessary to support this indication.

Furthermore, the submission lacks sufficient information to demonstrate that the proposed control strategy for the omeprazole and sodium bicarbonate active pharmaceutical ingredients (APIs) of this combination product meets the regulatory standard. As per the Integrated Quality Assessment (IQA) review, the proposed control strategy is insufficient to assure the identity, strength, purity, quality, and bioavailability of the drug product as required by 21 CFR 314.50. The methods to be used (b) (4) are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability (21 CFR 314.125(b)(1)).

Without sufficient information to support the characterization of the APIs in the product, a determination of the effectiveness of omeprazole and sodium bicarbonate for oral suspension cannot be supported. (b) (4)

No new safety signals were identified during review of the data submitted in support of the application; however, as a PPI, identified class safety concerns are applicable to omeprazole and sodium bicarbonate for oral suspension and should be presented in the proposed prescribing information (PI) for the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	(b) (4)	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	(b) (4)	• Omeprazole and sodium bicarbonate for oral suspension is a combination of omeprazole and sodium bicarbonate that can be administered to patients who experience difficulty in swallowing.
Benefit	• In study OME-RM02-001 omeprazole and sodium bicarbonate for oral suspension (40 mg/1680 mg) was found to have comparable bioavailability (BA) to Zegerid (omeprazole/sodium bicarbonate 40 mg/1680 mg) powder for oral suspension under fasting conditions. The 90% CI for the ratio of the geometric means of AUC0-t, AUC_{inf} and C_{max} were within the bioequivalence acceptance criteria of 80-125%. While the C_{max} trended lower relative to Zegerid, the geometric mean ratios fell within the he bioequivalence acceptance criteria of 80-125%. (b) (4	• The Applicant demonstrated that omeprazole and sodium bicarbonate for oral suspension (40 mg/1680 mg) has comparable bioavailability to Zegerid (omeprazole/sodium bicarbonate 40 mg/1680 mg) powder for oral suspension under fasting conditions. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4) (b) (4) • The Applicant did not submit data to support the administration of omeprazole and sodium bicarbonate for oral suspension by nasogastric or orogastric tube. • Data to support administration by nasogastric and orogastric tube is necessary to support the proposed indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients". • The submission lacks sufficient information to demonstrate that the proposed control strategy for the omeprazole and sodium bicarbonate APIs of this combination product meets the regulatory standard.	(b) (4) • The data presented in the application is not adequate to support the indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients". • As per the IQA review, the proposed control strategy is insufficient to assure the identity, strength, purity, quality, and bioavailability of the drug product as required by 21 CFR 314.50. • From the drug product and the manufacturing process review perspectives, this application cannot be recommended for approval until adequate controls for the APIs, sodium bicarbonate and omeprazole, are established, and the Applicant has demonstrated that drug product with the requisite quality can be manufactured consistently. • The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability (21 CFR 314.125(b)(1)).
Risk and Risk Management	• No clinically significant laboratory trends or changes in vital signs were observed during the study. • The available post marketing data, including findings from several epidemiological studies, suggest an increased risk of acute tubulointerstitial nephritis, *Clostridium difficile*-associated diarrhea, bone fractures (hip, wrist, and spine), cutaneous and systemic lupus erythematosus and electrolyte abnormalities such as hypomagnesemia and hypocalcemia in patients using proton pump inhibitors.	• No new safety signals were identified during review of the data submitted in support of the application; however, as a PPI, identified class safety concerns are applicable to omeprazole and sodium bicarbonate for oral suspension and should be presented in the proposed PI for the product.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		

	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
X	**Patient experience data was not submitted as part of this application.**		

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This is a 505(b)(2) NDA application that relies on FDA's previous findings of safety and effectiveness for the listed drugs (LD), Zegerid for oral suspension (NDA 021636) and Prilosec capsules (NDA 019810). The application includes a clinical study that evaluated the relative BA and pharmacokinetics (PK) of omeprazole and sodium bicarbonate for oral suspension (Konvomep 40 mg/1680 mg) compared to Zegerid powder for oral suspension (40 mg/1680 mg) and Omeprazole DR 40 mg capsules in healthy adult subjects. Omeprazole DR, an approved generic product and a reference listed drug in the Orange Book, was selected as an acceptable alternative for this study due to the discontinuation of Prilosec capsules.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-IND Meeting: June 2015

- The Agency stated that if the Sponsor chooses to rely on Prilosec and Zegerid, the Sponsor needs to establish a "bridge" (via comparative BA/PK data) between the proposed drug and listed drugs.
- The Agency recommended conducting a 3-arm relative bioavailability study that includes the proposed product, Prilosec, and Zegerid.
- The Agency also stated that the new product may trigger the Pediatric Research Equity Act (PREA) because of a new proposed dosing regimen.

Pre-NDA Meeting: September 2019

- The Agency and the Sponsor discussed both the nonclinical and clinical data, as well as general regulatory topics to support a 505(b)(2) NDA application for the new omeprazole and sodium bicarbonate for oral suspension.
- The Sponsor acknowledged sodium bicarbonate as an active ingredient in their product and agreed to update the draft labeling accordingly to be consistent with the labeling for the LD, Zegerid.
- The Agency agreed that no additional nonclinical studies are necessary provided that the Sponsor establish an adequate scientific bridge between the proposed product and each LD. The Sponsor will be required to justify the safety of all inactive ingredients present in the new product.
- The Agency stated that the adequacy of the relative BA trial results to establish a scientific bridge between the new product and each LD will be determined after the Agency has completed the formal review of the full study report and assessment of other factors including validation of the bioanalytical methods used in the PK study.

The Sponsor provided a schematic description of the planned comparative dissolution studies. The Agency stated that the proposed approach appeared reasonable; however, a determination of the adequacy of the dissolution profile would depend on a review of the dissolution data and method that is to be provided with the NDA.

Table 3. Amendments Received and Reviewed, NDA 213593

Sequence No.	Date of Submission	Description
0002	2020-04-14	Labeling update
0003	2020-04-17	Force replace NOA
0004	2020-04-21	Request for proprietary name review
0005	2020-05-15	Response to FDA information request
0006	2020-05-12	Response to FDA information request
0007	2020-06-11	Response to FDA information request
0008	2020-06-11	Response to FDA information request
0009	2020-06-26	Response to FDA information request
0010	2020-07-01	Quality amendment
0011	2020-07-06	Request for waiver for labeling requirements, response to FDA information request
0012	2020-08-04	Request for Comments and Advice, Response to FDA Information Request
0013	2020-07-31	120-day safety update
0014	2020-08-27	Response to FDA information request
0015	2020-08-28	Request for proprietary name review
0016	2020-09-15	Follow-up to response to information request (submitted on Jun 11, 2020)
0017	2020-09-03	Response to FDA information request
0018	2020-09-10	Withdrawal of conditionally approved proprietary name
0019	2020-09-11	Response to FDA information request
0020	2020-09-17	Response to FDA information request
0021	2020-09-24	Product correspondence: new patent information
0022	2020-09-21	Request for comments and advice
0023	2020-09-28	Response to FDA information request
0024	2020-09-25	Response to FDA information request
0025	2020-10-09	Response to information request
0026	2020-10-13	Response to information request
0027	2020-10-16	Follow-up to response to information request (submitted on Aug 27, 2020)
0028	2020-10-20	Response to information request
0029	2020-10-28	Response to information request
0030	2020-10-30	Follow-up to responses to information requests (submitted on June 11, September 15, September 17 and Sep 28, 2020) Response to information request (dated Oct 19, 2020)
0031	2020-11-20	Response to information request
0032	2020-12-04	Response to information request

Source: Clinical reviewer's table based on Applicant's submissions
Abbreviations: FDA, Food and Drug Administration; NOA, notice of acceptance

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No significant issues identified. The Division of New Drug Bioequivalence Evaluation in the Office of Study Integrity and Surveillance recommends accepting data without an on-site inspection for the clinical and analytical site as a recent inspection resulted in a No Action Indicated classification. See May 28, 2020 review by Ting Wang.

4.2. Product Quality

On review of the chemistry, manufacturing, and controls information provided in the original submission and reviewed amendments, Office of Pharmaceutical Quality finds that the proposed control strategy is insufficient to assure the identity, strength, purity, quality, and bioavailability of the drug product as required by 21 CFR 314.50. The submission lacks sufficient information to demonstrate that the proposed control strategy for the omeprazole and sodium bicarbonate APIs of this combination product meets the regulatory standard.

The strength of the API, sodium bicarbonate, in the drug product throughout the product shelf-life and during the in-use period is not adequately assured. The suitability of proposed assay method for the API sodium bicarbonate by (b) (4) has not been fully demonstrated. (b) (4) (b) (4) Thus, the method may be underestimating the amount of sodium bicarbonate at the high end and, more importantly, may be overestimating the amount of sodium bicarbonate at the low end. There are no data demonstrating that the diluent and constituted suspension will consistently meet the requisite sodium bicarbonate assay acceptance criterion of 90.0% to 110.0% of the LC at release and throughout the shelf-life. Similarly, there are no data to demonstrate that the constituted suspension will meet the 90.0% to 110.0% of the LC and throughout the 30-day in-use period. An in-process control for (b) (4) has not been established.

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

From the drug product and the manufacturing process review perspectives, this application cannot be recommended for approval until adequate controls for the APIs, sodium bicarbonate and omeprazole, are established, and the Applicant has demonstrated that drug product with the requisite quality can be manufactured consistently.

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

[redacted]

The currently proposed labeling does not conform to 21 CFR 201. However, labeling negotiations have not been completed during the current review cycle from chemistry, manufacturing, and controls perspective, and further review of labeling will be needed when the NDA is resubmitted.

Refer to the IQA in DARRTS for further details of the quality assessment.

The following product quality related deficiencies and recommendations for how to address the deficiencies will be communicated to the Applicant in the CR letter:

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

1) The strength of the active ingredient, sodium bicarbonate, in the drug product throughout the product shelf-life and during the in-use period is not adequately assured.
   a) The suitability of proposed assay method for the active ingredient sodium bicarbonate by [redacted] (b) (4)) has not been fully demonstrated. Specifically [redacted] (b) (4)

b) Thus, the method may be underestimating the amount of sodium bicarbonate at the high end and, more importantly, may be overestimating the amount of sodium bicarbonate at the low end. There are no data demonstrating that the diluent and constituted suspension will consistently meet the requisite sodium bicarbonate assay acceptance criterion of 90.0% to 110.0% of the label claim (LC) at release and throughout the shelf-life. Similarly, there are no data to demonstrate that the constituted suspension will meet the 90.0% to 110.0% of the LC and throughout the 30-day in-use period.

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

3) You have not established an in-process control for the (b) (4) (b) (4).

To Address These Deficiencies

1) Revise the specifications for the diluent and the constituted oral suspension to include the tests, analytical procedures, and acceptance criteria for the identification and assay of the active ingredient sodium bicarbonate. Update Diluent section 3.2.P.5.1 and Kit (Constituted Suspension) section 3.2.P.5.1 accordingly.

2) Provide evidence that analytical procedure (b) (4) is suitable for the intended use by demonstrating that the range of recoveries does not significantly overestimate or underestimate the bicarbonate measurement. Alternatively, revise the method to minimize the wide range in percent recovery.

3) Provide method validation reports for omeprazole assay procedures (b) (4) and MET-CDM-000025 and provide evidence of the comparability of the results obtained using each test.

4) Submit batch release data and a minimum of 6 months of long-term and accelerated stability data from at least one batch of each filling configuration (90 mL, 150 mL and 300 mL) of the diluent and the constituted suspension. Testing should be performed per the revised specifications that include the identification and assay of sodium bicarbonate. The drug product batches should be packaged in the to-be marketed container closure systems and manufactured at no less than 1/10th of the intended commercial scale. Submit in-use stability data for suspensions prepared from each of these stability batches.

5) The above-mentioned diluent batches should be manufactured per the manufacturing process and the revised control strategy including (b) (4) . Submit representative batch record in 3.2.R and update the corresponding sections of 3.2.P.3.3 if there is any change made (See Item #6 below).
6) To address Deficiency #3, provide the sampling plan (sampling number and the locations) and the acceptance criteria supported by batch data and in line with the acceptance criteria at the product release. Update 3.3.P.3.4 accordingly and include the in-process testing results.

Additional Comments

We have the following comments/recommendations that are not approvability issues:

1) With regard to the test for particle size distribution of the constituted suspension (Proc. No. 20-12-SP-2972), address the following comments.
   a) Provide a copy of Method Development Report No. 19-012-80800-R01 "Method Optimization Report for Particle Size Distribution of Omeprazole Oral Suspension, 2 mg/ml."
   b) (b) (4)
   c) Provide particle size distribution data for the constituted suspension during the in-use period.
2) Confirm the omeprazole bottle target fill weights and the diluent bottle target fill volumes required to prepare constituted suspensions meeting the label claim of 2 mg/mL omeprazole and 84 mg/mL sodium bicarbonate and the requisite deliverable volumes of 90, 150 and 300 mL, and provide clarification on how the target fill weights and volumes were determined.

4.3. Clinical Microbiology

No significant issues identified.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No nonclinical studies have been conducted with omeprazole or sodium bicarbonate by the Applicant. The Applicant is relying on FDA's findings of safety for Zegerid (NDA 021636) and Prilosec (NDA 019810) to support the nonclinical safety of omeprazole and sodium bicarbonate for oral suspension.

The maximum daily dose of omeprazole in the omeprazole and sodium bicarbonate for oral suspension is 40 mg. The proposed omeprazole oral suspension formulation contains 2 mg/mL of omeprazole which equals to a daily dosage of 20 mL. Omeprazole and sodium bicarbonate for oral suspension also contains 84 mg/mL of sodium bicarbonate which protects the omeprazole from gastric acid degradation. A daily dose of 20 mL omeprazole oral suspension results in a daily dose of 1680 mg sodium bicarbonate. The Applicant's proposed maximum daily doses of omeprazole and sodium bicarbonate are the same as those in the listed drug, Zegerid, 40 mg omeprazole/1680 mg of sodium bicarbonate. Therefore, there are no safety concerns for the levels of omeprazole and sodium bicarbonate in the omeprazole and sodium bicarbonate for oral suspension based on their presence at similar levels in the listed drug.

There are no safety concerns for the levels of impurities present in the omeprazole and sodium bicarbonate for oral suspension.

5.2. Referenced NDAs, BLAs, DMFs

This is a 505(b)(2) NDA application and relies on FDA's previous findings of safety and effectiveness for the LDs, Zegerid for oral suspension (NDA 021636) and Prilosec capsules (NDA 019810).

5.3. Pharmacology

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it 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.

5.4. ADME/PK

No pharmacokinetic studies have been conducted by the Applicant.

5.5. Toxicology

5.5.1. General Toxicology

The safety of omeprazole and sodium bicarbonate have been established previously by the innovators. The Applicant is relying on FDA's findings of safety for Zegerid (NDA 021636) and Prilosec (NDA 019810) to support the nonclinical safety of omeprazole and sodium bicarbonate for oral suspension.

5.5.2. Genetic Toxicology

Omeprazole was positive for clastogenic effects in an in vitro human lymphocyte chromosomal aberration assay, in one of two in vivo mouse micronucleus tests, and in an in vivo bone marrow cell chromosomal aberration assay. Omeprazole was negative in the in vitro Ames Test, an in vitro mouse lymphoma cell forward mutation assay, and an in vivo rat liver DNA damage assay.

5.5.3. Carcinogenicity

In a 24-month carcinogenicity study in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H2-receptor antagonists.

5.5.4. Reproductive and Developmental Toxicology

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at doses up to 69.1 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) during organogenesis did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 3.36 to 33.6 times an oral human dose of 40 mg on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 3.36 to 33.6 times an oral human dose of 40 mg on a body surface area basis), administered prior to mating through the lactation period.

5.5.5. Other Toxicology Studies

Safety Assessment of Excipients

There are no safety concerns for the levels of the excipients present in the omeprazole and sodium bicarbonate for oral suspension. The proposed formulation contains compendial and non-compendial excipients with well-established safety levels in the Agency's Inactive Ingredients Database (IID). The levels of each excipient in comparison to the levels included in the Agency's IID are shown in the table below. The non-compendial ingredient not included in the IID is the strawberry flavor (b) (4)

All flavoring ingredients contained in (b) (4) are considered Generally Recognized as Safe. (b) (4) (b) (4). Omeprazole and sodium bicarbonate for oral suspension contains (b) (4) Therefore, (b) (4) can be safely used at levels up to 4.0% (w/w) (about 1.1% w/v).

All flavoring ingredients contained in (b) (4) are considered Generally Recognized as Safe. (b) (4) (b) (4) Omeprazole and sodium bicarbonate for oral suspension contains (b) (4) Therefore, (b) (4) can be safely used at levels up to 4.0% (w/w) (about 1.1% w/v).

Table 4. Comparison of Omeprazole and Sodium Bicarbonate for Oral Suspension Ingredients to the Inactive Ingredients Database

Ingredient	Amount in Omeprazole Suspension Formulation	Inactive Ingredients Database[a] (Potency per Unit)
Benzyl Alcohol	(b) (4)	(b) (4)
Carboxymethylcellulose Sodium		
Poloxamer 188		
Simethicone Emulsion (b) (4)		

Ingredient	Amount in Omeprazole Suspension Formulation	Inactive Ingredients Database[a] (Potency per Unit)
Sodium Citrate (Dihydrate)	(b) (4)	(b) (4)
Sorbitol Solution		
Sucralose		
FD&C Red No. 40[c]		
Purified Water		

[a] Limit for an oral suspension unless otherwise noted.
(b) (4)
[c] FD&C Red No. 40 is a non-compendial ingredient but is included in the IID. Reference: 21 CFR 74.1340.

Source: The Applicant's non-clinical overview table 2.4-1 p. 1-2/3

Safety Assessment of Extractables/Leachables

A safety assessment of the potential extractables/leachables from the container/closure system in the omeprazole and sodium bicarbonate for oral suspension drug product was performed and did not raise a safety concern.

In the screening extractable study, an analytical threshold was set up based on the worst-case toxicological concern, dosage information, and experimental design, and all compounds detected above the analytical threshold were identified and semi-quantified. Several extractable compounds were detected in the (b) (4) Of the 24 elements analyzed in the extractable study, one (1) element was detected in the (b) (4) However, all elements were under the International Conference on Harmonisation Q3D limits. A toxicological assessment of the compounds identified in the extractable study was performed to identify extractables that could potentially pose a health risk. Among all the chemicals detected in the extractable study, only two chemicals (b) (4) were identified to have toxicological concerns and considered high priorities for further leachables assessment.

In the leachable study for the omeprazole and sodium bicarbonate for oral suspension aged for 30 days in (b) (4), samples were analyzed for volatile, semi-volatile, non-volatile organic compounds and inorganic elements by (b) (4) There was no volatile, semi-volatile, or non-volatile leachable identified for the omeprazole and sodium bicarbonate for oral suspension in either packaging configuration. (b) (4) were not detected as a leachable in the suspension.

Additionally, analysis of 25 elements detected several elements in the (b) (4) and labels for Omeprazole 0.2% Oral Suspension samples. All detected elements were (b) (4) However, all elements were under the International Conference on Harmonisation Q3D control limits for oral exposure (ppb), except for (b) (4) .

The maximum daily dose of omeprazole in the oral suspension formulation is 80 mg/day, which is equivalent to 40 mL of oral suspension formulation. The amount of Pb in the (b) (4) Thus, at the maximum daily dose of omeprazole (80 mg/day), there are no safety concerns for the potential exposure to Pb from the HDPE bottles.

6 Clinical Pharmacology

6.1. Executive Summary

In this NDA submission, the Applicant has requested approval for an omeprazole and sodium bicarbonate for oral suspension utilizing the 505(b)(2) regulatory pathway. The proposed product contains one bottle of omeprazole USP powder and one bottle of sodium bicarbonate USP in strawberry-flavored diluent. The product is to be constituted to oral suspension by the pharmacist before dispensing to the patient.

For the efficacy and safety of the proposed omeprazole and sodium bicarbonate for oral suspension, the Applicant has proposed to rely upon the Agency's prior findings of safety and efficacy for the listed drugs (LD), Zegerid (NDA 021636) and Prilosec (NDA 019810). The proposed indications and dosing regimens for omeprazole and sodium bicarbonate for oral suspension are the same as those for the listed drug, Zegerid.

To justify the reliance on the Agency's previous findings of safety and efficacy for Zegerid and Prilosec, the Applicant conducted a single dose, randomized, three-period, three-treatment, triple crossover study to evaluate the relative bioavailability and pharmacokinetics of a single oral dose of omeprazole and sodium bicarbonate for oral suspension (omeprazole/sodium bicarbonate, 40 mg/1680 mg), Zegerid (omeprazole/sodium bicarbonate, 40 mg/1680 mg) powder for oral suspension, and Omeprazole DR capsules USP, 40 mg (Sandoz, ANDA 076515, Reference Standard per Orange Book). As stated above, as 40 mg Prilosec capsules have been discontinued, the Applicant's use of Omeprazole DR capsules in the relative BA study is acceptable to support the proposed bridging to Prilosec.

The proposed product showed comparable systemic exposure of omeprazole and sodium bicarbonate for oral suspension 40 mg to that of Zegerid 40 mg meeting the bioequivalence criteria. The AUC of the proposed product was comparable to that of Omeprazole DR capsule 40 mg. Although the C_{max} of the proposed product exceeded that of Omeprazole DR capsule, it was sufficiently similar to the C_{max} of Zegerid to support the safety of the proposed product.

Through the study described above, the Applicant has adequately established the scientific bridge between the proposed omeprazole and sodium bicarbonate for oral suspension and Zegerid for the dose evaluated (40 mg omeprazole/1680 mg sodium bicarbonate) to justify the proposed reliance on the previous findings of safety and efficacy for the LD.

(b) (4)

(b) (4)

Additionally, the Applicant has proposed the indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients", as contained in the prescribing information (PI) for Zegerid. Data to support administration of omeprazole and sodium bicarbonate for oral suspension via nasogastric and orogastric tube is necessary to support this indication. Results from in-vitro studies to assess the suitability of administration via nasogastric or orogastric tube was not available at the time of the completion of this review. As a result, the information provided in this NDA is not adequate to support the administration of the proposed product via nasogastric or orogastric tube. Refer to the IQA for additional information.

Recommendations

The Division of Inflammation and Immune Pharmacology in the Office of Clinical Pharmacology has found the submission partially acceptable from a clinical pharmacology standpoint.

The clinical pharmacology data are adequate to recommend approval of the application with limited labeling claims for indication specific to the 40 mg dose of omeprazole administered orally that do not require the use of nasogastric or orogastric tube (i.e., treatment of active benign gastric ulcer).

(b) (4)

The following comments will be communicated to the Applicant in the CR letter:

(b) (4)

2) The information provided in this NDA and reviewed amendments is not adequate to support the proposed indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients". Data to support administration of omeprazole and sodium

bicarbonate for oral suspension via nasogastric and orogastric tube is necessary to support this indication.

6.2. Summary of Clinical Pharmacology Assessment

Relative Bioavailability Between Omeprazole and Sodium Bicarbonate for Oral Suspension (40 mg/1680 mg) Compared to Zegerid (Omeprazole/Sodium Bicarbonate Powder for Oral Suspension, 40 mg/1680 mg) and Omeprazole DR Capsules, 40 mg

The Applicant conducted an open-label, single dose, randomized, three-treatment, three-period, triple crossover, pharmacokinetic and bioavailability study (OME-RM02-001) of omeprazole and sodium bicarbonate for oral suspension, 40 mg/1680 mg, compared to Zegerid powder for oral suspension, 40 mg/1680 mg, and Omeprazole DR capsules, 40 mg, in healthy adult subjects under fasted conditions.

The Division of New Drug Bioequivalence Evaluation in the Office of Study Integrity and Surveillance recommends accepting relative BA study data without an on-site inspection for the clinical and analytical site as a recent inspection resulted in a No Action Indicated classification (Memo dated May 28, 2020 by Ting Wang in DARRTS).

Results from Study OME-RM02-001 indicated that omeprazole and sodium bicarbonate for oral suspension has bioavailability comparable to Zegerid suspension under fasting conditions. The 90% CI for the ratio of the geometric means of AUC0-t, AUC_{inf} and C_{max} were within the bioequivalence acceptance criteria of 80-125% (Table 5). While the C_{max} trends lower relative to Zegerid, the geometric mean ratios fall within the bioequivalence acceptance criteria of 80-125%. Further, the AUC is comparable between the omeprazole and sodium bicarbonate for oral suspension and Omeprazole DR. The safety of the higher C_{max} observed with administration of omeprazole and sodium bicarbonate for oral suspension relative to Omeprazole DR 40 mg is supported by the comparability to Zegerid.

The clinical pharmacology reviewer's independent analysis of the Applicant's data confirmed these results and supported the Applicant's conclusion. However, it must be noted that the results from this study only establishes a bridge between 40mg/1680mg dose of the Applicant's product and Zegerid 40 mg/1680 mg.

Table 5. Summary of Statistical Analysis of PK Comparisons (Fasted State) Between Omeprazole and Sodium Bicarbonate for Oral Suspension, 40 mg/1680 mg, Zegerid 40 mg/1680 mg, and Omeprazole DR Capsules 40 mg

	Treatment			90% Geometric CI of GMR	
Test Arm	**Comparison**	**Parameter**	**GMR**	**Lower**	**Upper**
Treatment A: Omeprazole and sodium bicarbonate for oral suspension, 40 mg (Test)	Treatment A – Treatment B (Zegerid – powder for oral suspension)	AUC_{0-t} (h*ng/mL)	100.36	95.50	105.47
		AUC_{0-inf} (h*ng/mL)	100.45	95.56	105.59
		C_{max} (ng/mL)	89.87	82.58	97.80
	Treatment A – Treatment C (Omeprazole – DR capsules)	AUC_{0-t} (h*ng/mL)	94.07	89.42	98.97
		AUC_{0-inf} (h*ng/mL)	93.48	88.80	98.41
		C_{max} (ng/mL)	161.53	148.09	176.19

Source: The Applicant's analysis adapted from Table 2.2, 2.3 and 2.4 from CSR for OME-RM02-001
Treatment A: Omeprazole and sodium bicarbonate for oral suspension (omeprazole/sodium bicarbonate, 40 mg/1680 mg) (Test);
Treatment B: Zegerid, 40 mg/1680 mg (Reference #1)
Treatment C: Omeprazole DR capsules USP, 40 mg (Reference #2)
Abbreviations: AUC_{0-t}, area under the plasma concentration to the last measurable concentration; AUC_{0-inf}, area under the plasma concentration versus time curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; DR, delayed-release; GMR, geometric mean ratio; PK, pharmacokinetic

The Applicant has not conducted a relative bioavailability study to assess the performance of their product in the presence of food. This is acceptable as the product is intended to be administered (b) (4) (b) (4)

(b) (4)

6.2.1. Clinical Pharmacokinetics

The Applicant assessed the single dose pharmacokinetics from the omeprazole and sodium bicarbonate for oral suspension as obtained from the open-label, 3-way crossover relative bioavailability study under fasting condition. Table 6 summarizes the pharmacokinetic parameters following dosing of omeprazole and sodium bicarbonate for oral suspension 40 mg/1680 mg, Zegerid 40 mg/1680 mg, and Omeprazole DR capsules 40 mg. Figure 3 illustrates the plasma concentration-time profile for omeprazole from each of the tested formulations.

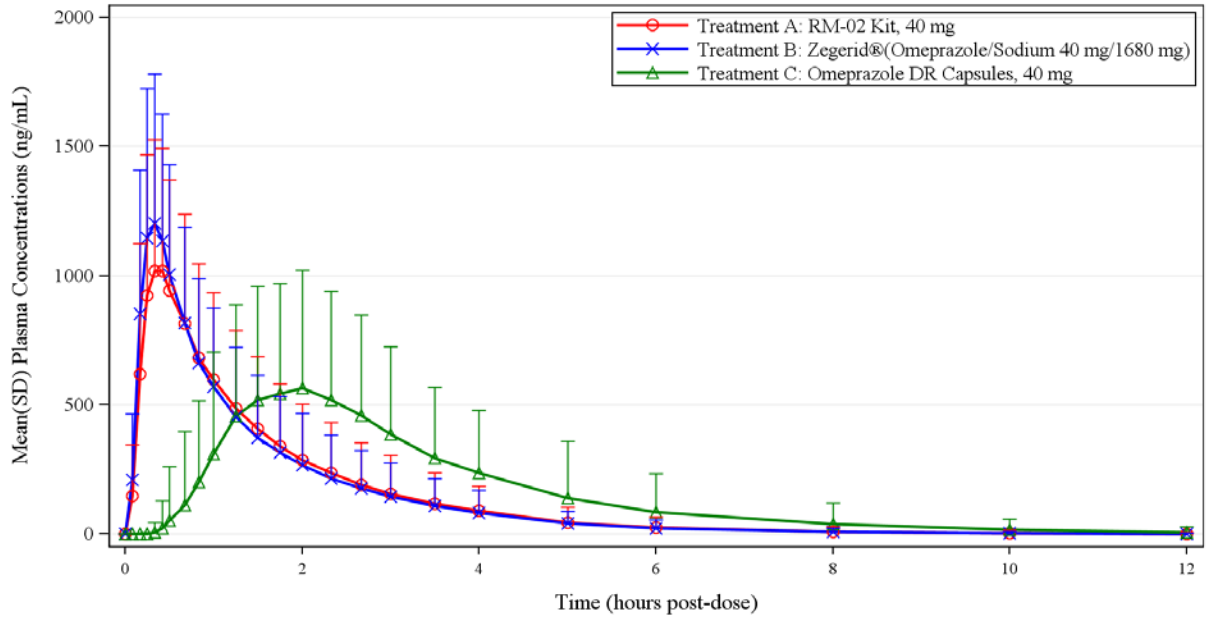
Overall, the results indicated that the pharmacokinetic parameters and plasma concentration time profiles of the omeprazole was comparable between omeprazole and sodium bicarbonate for oral suspension 40 mg/1680 mg and Zegerid 40 mg/1680 mg. However, the C_{max} was higher for the omeprazole and sodium bicarbonate for oral suspension and Zegerid relative to the Omeprazole DR capsules. While the C_{max} for the omeprazole and sodium bicarbonate for oral suspension appears to trend lower (1250 ng/mL vs 1390 ng/mL, 90 % GMR CI range of 83 - 97 %) relative to Zegerid, the AUC for all three formulations were generally comparable within the acceptability criterion for bioequivalence.

Table 6. Descriptive Summary of Mean PK Parameters Under Fasting Conditions for Omeprazole and Sodium Bicarbonate for Oral Suspension 40 mg/1680 mg, Zegerid 40 mg/1680 mg, and Omeprazole DR Capsules 40 mg

Parameter	Treatment A Omeprazole 40 mg (N=57)	Treatment B Zegerid 40/1680 mg (N=60)	Treatment C Omeprazole DR Capsules 40 mg (N=57)
AUC_{0-t} (h·ng/mL)	1640 (1050)	1630 (977)	1860 (1520)
AUC_{0-inf} (h·ng/mL)	1640 (1050)	1640 (981)	1900 (1570)
C_{max} (ng/mL)	1250 (470)	1390 (540)	853 (443)
T_{max} (h)	0.33 (0.17-1.30)	0.33 (0.17-0.67)	1.80 (0.50-6.00)
$t_{1/2}$ (h)[a]	1.07 (0.322)	1.02 (0.270)	1.14 (0.355)
K_{el} (1/h)	0.701 (0.191)	0.730 (0.208)	0.666 (0.204)
CL/F (L/h)	35.6 (21.7)	35.5 (21.8)	33.4 (22.7)
Vz/F (L)	48.0 (21.4)	45.8 (21.3)	47.3 (24.1)

Source: Table 11.2 from CSR for OME-RM02-001
Treatment A: Omeprazole and sodium bicarbonate for oral suspension, 40 mg/1680 mg
Treatment B: Zegerid 40 mg/1680 mg
Treatment C: Omeprazole DR, 40 mg
Abbreviations: AUC_{0-t}, area under the plasma concentration to the last measurable concentration; AUC_{0-inf}, area under the plasma concentration versus time curve extrapolated to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration; DR, delayed-release; K_{el}, terminal elimination rate constant; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration; Vz/F, apparent volume of distribution

Figure 3. Mean Omeprazole Plasma Concentrations (ng/mL) Versus Time Profiles From Study OME-RM02-001



Source: The Applicant's submitted table, the clinical study report p. 57/76

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant is seeking all of the approved indications listed under the LD, Zegerid, and the dosing regimens are consistent with the approved dosage for the LD. Table 7 below summarizes the dosing regimen proposed by the Applicant for each of the indications.

The proposed 40 mg dose for treatment of benign gastric ulcer or reduction of risk of upper gastrointestinal bleeding is appropriate and supported. However, data to support administration via nasogastric and/or orogastric tube is required to support the latter indication. The information provided in this NDA is not adequate to support the administration of omeprazole and sodium bicarbonate for oral suspension via nasogastric or orogastric tube (For additional details IQA, signed on January 26, 2021).

As discussed above, the proposed (b) (4)

Table 7. Proposed Dosage Regimens of Omeprazole and Sodium Bicarbonate for Oral Suspension by Indication for Adults 18 Years and Older

Indication	Recommended Dosage	Treatment Duration
(b) (4)		
Treatment of benign gastric ulcer	40 mg (20 mL) once daily	4 to 8 weeks
(b) (4)	(b) (4)	
(b) (4)		.
Reduction of risk of upper GI bleeding in critically ill patients	40 mg (20 mL) initially; followed by 40 mg 6 to 8 hours later; and 40 mg once daily thereafter	14 days

Source: Reviewer created table adapted from proposed PI submitted with NDA 213593
Abbreviations: (b) (4)

Therapeutic Individualization

The Applicant has not proposed any therapeutic individualization for their product in the PI based on intrinsic/extrinsic factors. This is consistent with the approved labeling language for the LDs (Zegerid and Prilosec).

Outstanding Issues

(b) (4)

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

No new clinical efficacy trials were submitted with this NDA. The Applicant has submitted a 505(b)(2) application relying on the Agency's previous findings of safety and efficacy for Zegerid and Prilosec as supported by study OME-RM02-001, an open-label, single dose, randomized, three-treatment, three-period, triple crossover, pharmacokinetic and bioavailability study of omeprazole and sodium bicarbonate for oral suspension (Konvomep) 40 mg/1680 mg, compared to Zegerid (omeprazole/sodium bicarbonate) powder for oral suspension 40 mg/1680 mg, and Omeprazole DR 40 mg capsules in healthy adult subjects under fasted conditions.

Table 8. Listing of Clinical Trials Relevant to this NDA, Study OME-RM02-001

Trial Identity	OME-RM02-001
Trial design	An open-label, single dose, randomized, three-treatment, three-period, triple crossover
Regimen/schedule/route	A single oral dose of one of the three study drugs. Treatment A: Konvomep (omeprazole/sodium bicarbonate oral suspension), 40 mg/1680 mg Treatment B: Zegerid (omeprazole/sodium bicarbonate oral suspension), 40 mg/1680 mg Treatment C: Omeprazole DR capsules, 40 mg
Study endpoints	Primary PK endpoints: Maximum plasma omeprazole concentration (C_{max}), the area under the plasma omeprazole concentration to the last measurable concentration (AUC_{0-t}), and area under the plasma omeprazole concentration versus time curve extrapolated to infinity (AUC_{0-inf}) Secondary PK endpoints: Time to C_{max} (T_{max}), apparent volume of distribution (Vz/F), apparent clearance (CL/F), terminal elimination rate constant (K_{el}), and elimination half-life ($t_{½}$) The safety and tolerability of a single oral dose of all omeprazole formulations
Treatment duration/follow up	16 days A single dose of one of the three study drugs with 7-day washout period
No. of patients enrolled	60
Study population	Healthy volunteers
No. of centers and countries	Single center, USA

Source: Clinical reviewer's table, adapted from the Applicant's clinical study report
Abbreviations: DR, delayed-release; NDA, new drug application; PK, pharmacokinetic; USA, United States of America

7.2. Review Strategy

The clinical review of this 505(b)(2) application focused on the ability of the submitted data to support reliance on the proposed LD, the safety data from the conducted study, and the acceptability of the proposed prescribing information.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial OME-RM02-001: An Open-Label, Single Dose, Randomized, Three-Treatment, Three-Period, Triple Crossover, Pharmacokinetic and Bioavailability Study of Omeprazole and Sodium Bicarbonate for Oral Suspension, 40 mg/1680 mg Compared to Zegerid (Omeprazole/Sodium Bicarbonate) Powder for Oral Suspension, 40 mg/1680 mg and Omeprazole Delayed-Release Capsules, 40 mg in Healthy Adult Subjects Under Fasted Conditions

Study Objectives

Primary: To evaluate relative bioavailability (BA) by comparing the ratio of the omeprazole and sodium bicarbonate for oral suspension 40 mg/1680 mg with respect to Zegerid powder for oral suspension, 40 mg/1680 mg. In addition, the geometric mean ratio of C_{max} for omeprazole and sodium bicarbonate for oral suspension, 40 mg/1680 mg to Zegerid powder for oral suspension, 40 mg/1680 mg was compared to the ratio of Zegerid to Omeprazole DR capsules, 40 mg under fasted conditions in healthy adult male and female subjects.

Secondary: To evaluate the safety and tolerability of a single oral dose of each of the omeprazole formulations in healthy adult male and female subjects.

Trial Design

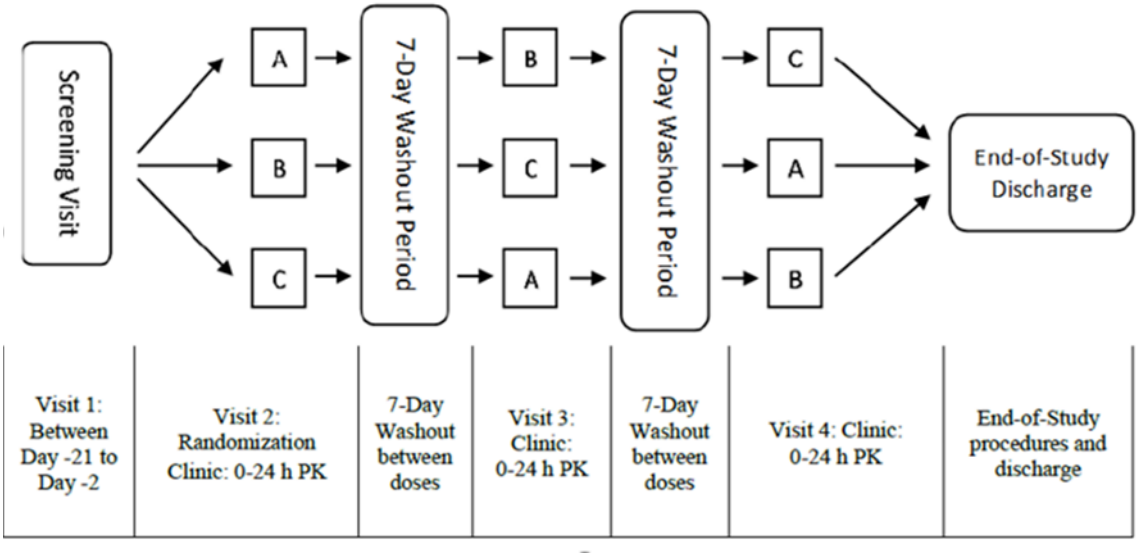
An open-label, single dose, randomized, three-treatment, three-period, triple crossover, pharmacokinetic and bioavailability study of omeprazole and sodium bicarbonate for oral suspension 40 mg/1680 mg compared to Zegerid (omeprazole/sodium bicarbonate) powder for oral suspension, 40 mg/1680 mg and Omeprazole DR capsules, 40 mg in healthy adult subjects under fasted conditions.

- Treatment A: Test formulation- Omeprazole and sodium bicarbonate for oral suspension 40 mg/1680 mg
- Treatment B: Reference formulation 1-Zegerid (omeprazole/sodium bicarbonate oral suspension), 40 mg/1680 mg
- Treatment C: Reference formulation 2- Omeprazole DR capsules, 40 mg

Trial OME-RM02-001 consisted of up to 21 days of screening period. After randomization, eligible subjects received single oral doses of one of the three study drugs (Treatment A, B, or C) on three separate occasions in a randomly assigned sequence, with each treatment separated by a minimum 7-day washout period. Total study participation was approximately 16

days. Subjects were confined to the Clinical Research Unit for three study periods, for approximately two days overnight stays for each period. Trial design is illustrated in Figure 4.

Figure 4. Overview of Trial Design



Source: The Applicant's clinical study report p.24/76
Treatment A: Omeprazole and sodium bicarbonate for oral suspension, 40 mg/1680 mg
Treatment B: Zegerid (omeprazole/sodium bicarbonate oral suspension), 40 mg/1680 mg
Treatment C: Omeprazole DR capsules, 40 mg
Abbreviations: h, hour; PK, pharmacokinetic

For details on the trial design, endpoints, statistical analysis plan, study results, and demographics, see Section 15.3 OCP Appendices below.

Protocol Amendments

One protocol amendment was issued before any subjects were enrolled into the study.

The protocol was revised from Version 1 (February 23, 2017) to Version 2 (August 30, 2018) with the following changes:

- The number of subjects was increased from 15 to 60
- The evaluation of relative bioavailability was clarified
- Deleted "urine" from pregnancy test at Screening, added estradiol test for postmenopausal females at Screening to confirm status, and deleted FSH value (≥ 40 mIU/mL) for confirmation of status.
- Sample size determination was updated to support the increased number of subjects
- A definition of the Bioavailability Population was added and the planned PK/statistical analysis for the relative bioavailability analysis was updated and clarified.
- A definition of the Bioavailability Population was added and the planned PK/statistical analysis for the relative bioavailability analysis was updated and clarified.

- With respect to the planned statistical analysis, the protocol stated in the objectives section that an additional comparison would be made between the ratio of RM-02 (Treatment A) relative to Zegerid (Treatment B) and the ratio of Zegerid (Treatment B) relative to Omeprazole DR capsules (Treatment C). In Section 12.4 of the protocol, an additional comparison was described between the ratio of RM-02 (Treatment A) relative to Omeprazole DR capsules (Treatment C) and the ratio of Zegerid (Treatment B) relative to Omeprazole DR capsules (Treatment C).
- The statistical analysis plan clarified abovementioned two additional comparisons and included both in the analysis section; thus, three ratios were created (Treatment A: Treatment B; Treatment A:Treatment C; and Treatment B:Treatment C), and comparisons of the upper bounds of the 90% CI for the ratios were performed as follows:
    - Treatment A: Treatment B vs. Treatment B: Treatment C
    - Treatment A: Treatment C vs. Treatment B: Treatment C

Compliance with Good Clinical Practices

The Applicant attested that studies were conducted in compliance with Good Clinical Practice.

Financial Disclosure

No reportable financial conflicts of interest between the Applicant and any investigator involved in the conduct of the studies contained in the application.

Patient Disposition

A total of 60 eligible subjects were randomized in the study, and 55 subjects (91.7%) completed study treatment per protocol; 60 subjects (100.0%) were included in the PK Population, 57 subjects (95.0%) were included in the BA Population, and all 60 subjects (100.0%) were included in the Safety Population.

Protocol Violations/Deviations

According to the Applicant there was a total of 8 (13.3%) subjects with protocol deviations; they were considered minor and did not affect the overall quality and integrity of the study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All doses of study drug were administered by study site personnel and an oral cavity check was performed to confirm oral dosing. The date and time that study drug was administered to each subject were recorded.

None of the study subjects reported any prior medication use. Eleven subjects reported concomitant medication use. Of these, ten subjects were on contraceptive treatment and continued to use during the study period, and one subject used non-steroidal anti-inflammatory drug (ibuprofen) for toothache.

8.1.2. Assessment of Effectiveness

No efficacy studies were conducted to support this NDA. The determination of efficacy is based on the Applicant's demonstration of comparable BA to the LD. For details of the omeprazole pharmacokinetic parameters, see Section 6.2 Summary of Clinical Pharmacology Assessment above.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review of this NDA application focuses primarily on the data from the OME-RM02-001 study conducted in healthy adult subjects. The safety profile of omeprazole is well-characterized, and it has been approved for the treatment of GERD since 1989.

The safety parameters included adverse events (AEs), clinical laboratory parameters, physical exam findings, electrocardiogram (ECG) and vital signs. An AE that occurred during the study period was considered a treatment-emergent adverse event (TEAE). All subjects who received at least one dose of study drug were included in the safety analysis.

The safety parameters included AEs, clinical laboratory parameters, physical exam findings, ECG and vital signs. An AE that occurred during the study period was considered a TEAE. All subjects who received at least one dose of study drug were included in the safety analysis.

8.2.2. Review of the Safety Database

Overall Exposure

All 60 subjects received at least one dose of study drug and were included in the safety analysis. In the study, 57 subjects received a single oral dose of omeprazole and sodium bicarbonate for oral suspension (RM-02) 40 mg/1680 mg (Treatment A), 60 subjects received a single oral dose of Zegerid 40 mg/1680 mg (Treatment B), and 57 subjects received a single oral dose of Omeprazole DR capsule, 40 mg (Treatment C).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues were identified regarding data integrity and submission quality for the clinical study.

8.2.4. Safety Results

Deaths

No deaths were reported during the study.

Serious Adverse Events

No serious adverse events were reported during the study.

Dropouts and/or Discontinuations Due to Adverse Effects

One subject (b) (6) developed a tooth abscess unrelated to study treatment and was discontinued from the study due to the AE, based on the Investigator's decision to refer the subject to a dentist for treatment.

Three subjects requested to be withdrawn from the study and one subject needed to use a concomitant drug that was prohibited by the protocol.

Significant Adverse Events

No AEs of moderate or severe intensity were reported during the study.

Treatment Emergent Adverse Events and Adverse Reactions

Single oral doses of omeprazole and sodium bicarbonate for oral suspension (Konvomep), 40 mg/1680 mg, Zegerid 40 mg/1680 mg and Omeprazole DR capsules, 40 mg, were well tolerated by the adult male and female subjects.

Total of 13 treatment emergent adverse events (TEAEs) in 10 subjects (16.7%) were reported during the trial period.

- Treatment A: Omeprazole and sodium bicarbonate for oral suspension, 40 mg/1680 mg: 3 TEAEs in 2 subjects
- Treatment B: Zegerid (omeprazole/sodium bicarbonate oral suspension), 40 mg/1680 mg: 8 TEAEs in 6 subjects
- Treatment C: Omeprazole DR capsules, 40 mg: 2 TEAEs in 2 subjects

The most commonly reported TEAEs were headache and elevation of blood glucose increase, each event occurred in three (5%) subjects. Blood glucose was increased in one subject in the omeprazole and sodium bicarbonate for oral suspension group and two subjects in the Omeprazole DR group. Headache occurred in one subject in the omeprazole and sodium bicarbonate for oral suspension group and two subjects in the Zegerid group. In the Zegerid treatment group somnolence, nausea, eye pruritus, fatigue, toothache, and tooth abscess were each reported by one subject. All AEs were reported as mild in intensity; the majority of AEs (9

of the reported 13) were considered possibly related to treatment by the Investigator except for toothache, tooth abscess, vomiting, and 1 report of headache which were considered unlikely or not related to treatment by the Investigator.

Reported events occurred at similar rates across the assigned treatment groups, and no trends were observed on evaluation of adverse event data. Although the ability of the study to identify concerns was limited by both the small number of patients studied and single-dose exposure, no other safety concerns were identified by the Applicant or on FDA review of the study data.

Table 9. Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment, Safety Population

System Organ Class Preferred Term	Treatment A RM-02 Omeprazole and Sodium Bicarbonate for Oral Suspension 40/1680 mg (N=57) n (%)	Treatment B Zegerid 40/1680 mg (N=60) n (%)	Treatment C Omeprazole DR Capsules 40 mg (N=57) n (%)	All Subjects (N=60) n (%)
Number of AEs	3	8	2	13
Subjects with at least one TEAE	2 (3.5)	6 (10.0)	2 (3.5)	10 (16.7)
Nervous system disorders	1 (1.8)	3 (5.0)	0	4 (6.7)
Headache	1 (1.8)	2 (3.3)	0	3 (5.0)
Somnolence	0	1 (1.7)	0	1 (1.7)
Gastrointestinal disorders	1 (1.8)	2 (3.3)	0	3 (5.0)
Nausea	0	1 (1.7)	0	1 (1.7)
Toothache	0	1 (1.7)	0	1 (1.7)
Vomiting	1 (1.8)	0	0	1 (1.7)
Investigations	1 (1.8)	0	2 (3.5)	3 (5.0)
Blood glucose increased	1 (1.8)	0	2 (3.5)	3 (5.0)
Eye disorders	0	1 (1.7)	0	1 (1.7)
Eye pruritus	0	1 (1.7)	0	1 (1.7)
General disorders and administration site conditions	0	1 (1.7)	0	1 (1.7)
Fatigue	0	1 (1.7)	0	1 (1.7)
Infections and infestations	0	1 (1.7)	0	1 (1.7)
Tooth abscess	0	1 (1.7)	0	1 (1.7)

Source: The Applicant's submitted table, the clinical report p. 64/76. The results confirmed by the clinical reviewer by using Trial OME-RM02-001 adae.xpt. dataset
Note: Subjects are counted once for each system organ class and once for each preferred term.
N = number of subjects in the specified study population under each treatment;
n (%) = number and percent of subjects in the specified group.
Treatment A: Omeprazole and sodium bicarbonate for oral suspension (RM-02), 40/1680 mg (Test);
Treatment B: Zegerid (omeprazole/sodium bicarbonate oral suspension, 40 mg/1680 mg (Reference #1);
Treatment C: Omeprazole DR capsule, 40 mg (Reference #2).
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event

Laboratory Findings

Hematology

No clinically significant findings or changes in hematology laboratory values were reported during the study.

Chemistry

No clinically significant findings or changes in chemistry laboratory values were reported during the study. Three subjects, one subject taking omeprazole and sodium bicarbonate for oral suspension and two subjects taking omeprazole DR capsule, were noted to have mildly elevated blood glucose (less than 126 mg/dL); these glucose elevations were reported as TEAEs by the Investigator as possibly related to study treatment.

Urinalysis

No clinically significant urinalysis findings were reported during the study.

Physical Examinations

No clinically significant PE findings were noted for any subject.

Vital Signs

No clinically significant findings or changes in vital signs were reported during the study.

Electrocardiograms

No clinically significant ECG findings reported on the screening ECGs.

8.2.5. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data from postmarket use of PPIs have resulted in several class safety labeling updates (i.e.., acute tubulointerstitial nephritis, *Clostridium difficile*-associated diarrhea, bone fractures (hip, wrist, and spine), cutaneous and systemic lupus erythematosus, and electrolyte abnormalities (e.g., hypomagnesemia and hypocalcemia).

These identified class safety concerns are applicable to omeprazole and sodium bicarbonate for oral suspension and should be presented in the proposed PI for the product.

These identified class safety concerns are applicable to omeprazole and sodium bicarbonate for oral suspension and should be presented in the proposed PI for the product.

8.2.6. Integrated Assessment of Safety

As a single study was submitted to support this application, this section is not applicable.

8.3. Conclusions and Recommendations

No safety concerns were identified during review of the safety data from Study OME-RM02-001. In addition to the safety information proposed by the Applicant as reflected in the PI for the LD at time of NDA submission, updates were recommended to the proposed PI to reflect the recent class labeling update for acute tubulointerstitial nephritis for PPIs.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee was not held, and no external consultants were involved during the review of this NDA application.

10 Pediatrics

This application did not include an assessment or requested indication for pediatric patients.

Under the Pediatric Research Equity Act (PREA) (21 U. S. C. 335), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. (b) (4)

(b) (4)

(b) (4)

(b) (4)

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant's proposed labeling was reviewed, and recommended revisions and comments have been communicated to the Applicant during the review of this NDA. However, agreement was not reached during the review cycle, and additional labeling negotiations will be needed upon receipt of the Applicant's response to the Complete Response action.

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS are necessary as a result of the review of this NDA application.

13 Postmarketing Requirements and Commitment

Post-marketing requirements will be determined upon receipt of a subsequent submission to address the deficiencies noted during the review of this application.

14 Division Director (Clinical) Comments

I concur with the recommendation of the review team to issue a Complete Response letter for NDA 213593. This is a 505(b)(2) application that relies on FDA's previous findings of safety and effectiveness for the listed drugs (LD), Zegerid (omeprazole/sodium bicarbonate) for oral suspension and Prilosec (omeprazole DR capsules). The proposed product contains 2 mg omeprazole and 84 mg sodium bicarbonate per mL and is to be constituted to oral suspension by the pharmacist before dispensing to the patient. (b) (4)

I agree with the review team that this application in its present form is not adequate to support approval as the proposed control strategy is insufficient to assure the identity, strength, purity, quality, and bioavailability (BA) of the drug product as required by 21 CFR 314.50. The submission lacks sufficient information to demonstrate that the proposed control strategy for the omeprazole and sodium bicarbonate active ingredients of this combination product meets the regulatory standard.

In addition, while the Applicant has adequately established the scientific bridge between the proposed product and Zegerid at the dose of 40 mg (both containing 40 mg omeprazole and 1680 mg sodium bicarbonate) to justify the proposed reliance on the previous findings of safety and efficacy for the LD, the information provided in this NDA is not adequate to support (b) (4)

Without sufficient information to support the characterization of the active ingredients in the product, a determination of the effectiveness of the proposed product cannot be supported. (b) (4) Additionally, the information provided in this NDA is not adequate to support the proposed indication of "reduction of risk of upper gastrointestinal bleeding in critically ill patients", as contained in the PI for Zegerid. Data to support administration of the proposed product via nasogastric and orogastric tube is necessary to support this indication.

No new safety signals were identified during review of the data submitted in support of the application; however, as a PPI, identified class safety concerns are applicable and should be included in the proposed PI for the proposed product, when the application is approvable.

The agreement on final product labeling could not be reached during this review cycle; further negotiation will be continued at the time of resubmission. Postmarketing requirements and commitments, if deemed appropriate, will also be communicated at that time.

15 Appendices

15.1. References

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15.2. Financial Disclosure

Table 10. Financial Disclosure Covered Clinical Study OME-RM02-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

The Applicant conducted one clinical study for the omeprazole and sodium bicarbonate for oral suspension clinical development program (Study OME-RM02-001). Study OME-RM02-001 was an open-label, single dose, randomized, three-period, three-treatment, triple crossover study to evaluate the relative bioavailability and pharmacokinetics of a single oral dose of omeprazole and sodium bicarbonate for oral suspension (omeprazole/sodium bicarbonate, 40/1680 mg) (Test Formulation, Treatment A), Zegerid (omeprazole/sodium bicarbonate) powder for oral suspension, 40 mg/1680 mg (Reference Formulation #1, Treatment B), and Omeprazole DR Capsules, 40 mg (Reference Formulation #2, Treatment C) under fasted conditions in healthy male and female subjects.

Results from this comparative relative BA study was used to provide a scientific "bridge" to the Agency's finding of safety and efficacy for the listed drug (LD).

Table 11. Study Information (Study OME-RM02-001)

Study Title An Open-Label, Single Dose, Randomized, Three-Treatment, Three-Period, Triple Crossover, Pharmacokinetic and Bioavailability Study of Omeprazole and Sodium Bicarbonate for Oral Suspension (RM-02), 40 mg Compared to Zegerid (omeprazole/sodium bicarbonate) Powder for Oral Suspension, 40 mg/1680 mg and Omeprazole Delayed-Release Capsules USP, 40 mg in Healthy Adult Subjects Under Fasted Conditions	
Project No.	OME-RM02-001
Qualified Investigator	Alexander N. Prezioso, MD
Study Centres Clinical, Statistical, and Analytical:	Frontage Clinical Services, Inc. Clinical Research Center 200 Meadowlands Parkway Secaucus, New Jersey 07094 USA [redacted]

Source: Bioanalytical report for study OME-RM02-001

Table 12. Study Sample Information, Study OME-RM02-001

Description	Subject/Sample Information	No. of Samples
Total number of study samples expected per the protocol	60 subjects, 24 samples collected per subject per period	4320
Total number of study samples received	60 subjects	4176 primary samples 4176 back-up samples
Total number of primary study samples not received	All samples from group 2 period 2 for subject 1023; All samples from group 2 period 3 for subjects 1023, 1029 and 1045; All samples from group 3 period 3 for subjects 1050 and 1056	144 primary samples
Total number of study samples analyzed	Refer to Table 6 for the samples analyzed.	4176 primary samples

Source: Bioanalytical report for study OME-RM02-001

Table 13. Study Sample Storage and Handling, Study OME-RM02-001

Storage Temperature:	-20ºC
First date of analysis to last date of analysis:	Nov 28, 2018 to Dec 12, 2018
Duration of sample storage: (first collection date (PK1) to last extraction date)	Oct 23, 2018 to Dec 12, 2018

Source: Bioanalytical report for study OME-RM02-001

Table 14. Study Product Information, Study OME-RM02-001

Product	Test	Listed drug	Listed drug
Treatment identification	A	B	C
Product name	Omeprazole and sodium bicarbonate for oral suspension (40 mg/1680 mg)	Zegerid (Omeprazole /Sodium Bicarbonate) powder for oral suspension, 40 mg/1680 mg)	Omeprazole delayed-release capsules USP, 40 mg
Manufacturer	(b) (4)		
Strength	40 mg, 2 mg/mL constituted	40 mg, 2 mg/mL	40 mg
Dosage form	For oral suspension	Powder for oral suspension	Capsules
Dose administered	1 x 40 mg	1 x 40 mg	1 x 40 mg
Route of administration	Oral	Oral	Oral

Source: CSR for study OME-RM02-001

Study Design

This was an open-label, single dose, randomized, three-period, three-treatment, triple crossover study to evaluate the relative bioavailability and pharmacokinetics of a single oral dose of omeprazole and sodium bicarbonate for oral suspension (RM-02), 40 mg/1680 mg (Test Formulation, Treatment A), Zegerid, 40 mg/1680 mg (Reference Formulation #1, Treatment B), and Omeprazole DR capsules, 40 mg (Reference Formulation #2, Treatment C) under fasted conditions in healthy male and female subjects.

Following a screening period of up to 21 days, a total of 60 healthy, non-smoking, adult, male and female subjects were enrolled and randomized to receive study drug. Eligible subjects received single oral doses of one of three study drugs (Treatment A, B, or C) on three separate occasions in a randomly assigned sequence, with each treatment separated by a minimum 7-day washout period.

Table 15. Treatment Description

Treatment	Treatment Description
A	Test formulation: single oral dose of omeprazole and sodium bicarbonate for oral suspension (RM-02), 40 mg
B	Reference formulation #1: single oral dose of Zegerid (omeprazole/sodium bicarbonate) powder for oral suspension, 40 mg/1680 mg
C	Reference formulation #2: Single oral dose of omeprazole delayed-release capsules USP, 40 mg

Source: The Applicant's submitted table, CSR, p. 25/76.

In each study period (Day 1 of Periods 1, 2 and 3), dosing occurred in the morning after an overnight fast of at least 10 hours. Each subject was randomized to one of three treatment sequences (ABC, BCA, or CAB) in Periods 1, 2 and 3, respectively, with 20 subjects per sequence, according to a randomization schedule prepared prior to the start of the study. In each study period, serial pharmacokinetic (PK) blood samples (4 mL blood per sample) to measure plasma omeprazole concentrations were collected by direct venipuncture or by use of an indwelling cannula prior to dosing (0 hours, up to 60 minutes prior to dosing), and 5, 10, 15, 20, 25, 30, 40, 50 minutes post-dose and then at 1 hr, 1 hr 15 min, 1 hr 30 min, 1 hr 45 min, 2.0 hr, 2 hr and 20 min, 2 hr and 40 min, 3 hr, 3 hr and 30 min, then at 4, 5, 6, 8, 10, and 12 hours post-dose. During each of the 3 study periods, confinement was to begin at approximately 14:00 hours on the day prior to dosing and until 24 hours post dose.

Reviewer's comments: The bioequivalence (BE) study design is adequate to compare the relative bioavailability at the 40 mg dose. (b) (4)

The plasma elimination half-life of omeprazole after oral administration ranged between 0.5 to 1 hours based on the USPI for Prilosec. The washout period (7 days) was longer than 5 half-lives and appropriate.

The sampling time for the study is acceptable considering the half-life of omeprazole.

Study Results

Subject Disposition and Demographics:

A total of 60 eligible subjects were randomized in the study which included 49 males and 11 females. Table 16 below summarizes the demographics and body measurement data of the subjects who were randomized in the study.

Table 16. Summary of Demographics and Body Measurements Data of Subjects Included in the Pharmacokinetic Population

Parameter	Sequence ABC (N=20)	Sequence BCA (N=20)	Sequence CAB (N=20)	All Subjects (N=60)
Age (years)				
n	20	20	20	60
Mean (SD)	34.4 (4.52)	35.5 (7.63)	31.0 (5.99)	33.6 (6.38)
Median	34.5	35.5	31.0	34.0
Min, max	24, 43	23, 45	23, 43	23, 45
Gender, n (%)				
Male	17 (85.0)	17 (85.0)	15 (75.0)	49 (81.7)
Female	3 (15.0)	3 (15.0)	5 (25.0)	11 (18.3)
Race, n (%)				
Black or African American	12 (60.0)	13 (65.0)	14 (70.0)	39 (65.0)
White	8 (40.0)	7 (35.0)	4 (20.0)	19 (31.7)
American Indian or Alaskan Native	0	0	2 (10.0)	2 (3.3)
Ethnicity, n (%)				
Hispanic or Latino	6 (30.0)	8 (40.0)	6 (30.0)	20 (33.3)
Not Hispanic or Latino	14 (70.0)	12 (60.0)	14 (70.0)	40 (66.7)
Weight (kg)				
n	20	20	20	60
Mean (SD)	80.11 (6.945)	78.57 (8.932)	73.56 (11.505)	77.41 (9.583)
Median	79.75	77.70	74.30	78.40
Min, max	64.1, 98.2	63.6, 94.1	55.5, 90.0	55.5, 98.2
Height (cm)				
n	20	20	20	60
Mean (SD)	173.53 (7.665)	174.23 (7.380)	170.55 (8.028)	172.77 (7.733)
Median	175.50	173.00	173.00	174.00
Min, max	162.0, 191.0	157.0, 186.0	157.0, 182.5	157.0, 191.0
BMI (kg/m^2)				
n	20	20	20	20
Mean (SD)	26.65 (2.247)	25.86 (2.261)	25.18 (2.620)	25.90 (2.419)
Median	26.85	25.95	25.20	25.95
Min, max	21.7, 29.8	21.3, 29.8	19.6, 29.1	19.6, 29.8

Source: The Applicant's submitted table, CSR Table 11-1 p. 54/76.
N = number of subjects in the specified study population under each treatment;
n (%) = number and percent of subjects in the specified group.
Abbreviation: BMI, body mass index

Of the 60 subjects randomized to the study, 55 subjects (91.7%) completed study treatment per protocol; 60 subjects (100.0%) were included in the PK Population, 57 subjects (95.0%) were included in the BA Population, and all 60 subjects (100.0%) were included in the Safety Population. Three subjects did not receive at least one of the test or reference formulations and were not included in the BE analysis (Subjects # (b) (6)). Table 17 below summarizes the subject disposition by sequence and treatments.

Table 17. Subject Disposition by Sequence and Treatment, All Randomized Subjects

Subject Disposition	Sequence ABC (N=20) n (%)	Sequence BCA (N=20) n (%)	Sequence CAB (N=20) n (%)	All Subjects (N=60) n (%)
Randomized	20 (100.0)	20 (100.0)	20 (100.0)	60 (100.0)
Completed study	18 (90.0)	17 (85.0)	20 (100.0)	55 (91.7)
Discontinued study	2 (10.0)	3 (15.0)	0	5 (8.3)
Subject requests to be withdrawn from study	0	3 (15.0)	0	(3 (5.0)
Need for prohibited concomitant medication	1 (5.0)	0	0	1 (1.7)
Principal investigator decision – subject had tooth abscess, referred to dentist by PI	1 (5.0)	0	0	1 (1.7)
Safety population	20 (100.0)	20 (100.0)	20 (100.0)	60 (100.0)
Pharmacokinetic population	20 (100.0)	20 (100.0)	20 (100.0)	60 (100.0)
Bioavailability population	20 (100.0)	17 (85.0)	20 (100.0)	57 (95.0)

Population	Treatment A RM-02 Kit Omeprazole, 40 mg (N=57) n (%)	Treatment B Zegerid 40/1680 mg (N=60) n (%)	Treatment C Omeprazole DR Capsules, 40 mg (N=57) n (%)	All Subjects (N=60) n (%)
Safety population	57 (100.0)	60 (100.0)	57 (100.0)	60 (100.0)
Pharmacokinetic population	57 (100.0)	60 (100.0)	57 (100.0)	60 (100.0)
Bioavailability population	57 (100.0)	57 (95.0)	55 (96.5)	57 (95.0)

Source: The Applicant's submitted table, CSR, Table 10-1 p. 52/76.
N = number of subjects in the specified study population under each treatment;
n (%) = number and percent of subjects in the specified group.
Abbreviation: PI, principal investigator

Reviewer's comments: The demographics profile of the subjects enrolled in the study is acceptable.

Bioanalytical Methods and Validation

Omeprazole in plasma samples from the study were measured using a validated assay based on high performance liquid chromatography with tandem mass spectrometry detection. Details of the analytical method and summary of the validation are summarized in Table 18.

Reviewer's comments: The pre-study validation of the bioanalytical method used for the pivotal bioequivalence study is acceptable. The accuracy, precision, selectivity, sensitivity and stability

of the bioanalytical method were assessed in the method validation and are within the FDA-accepted ranges.

Table 18. Method Validation Summary

Report location	Central Data Room at (b) (4)			
Method description	Method BTM-2737-R0 is an LC-MS/MS method for the determination of omeprazole in K_2EDTA human plasma using omeprazole-d_3 as the internal standard (IS). Omeprazole and the internal standard were extracted by protein precipitation (PPT) from human plasma with acetonitrile. Reversed-phase HPLC separation was achieved with a Phenominex, Synergi 4µ Hydro-RP 80A (2.0 x 50 mm, 4.0 micron). MS/MS detection was set at mass transitions of m/z 346.2→198.1 for omeprazole and m/z 349.2→198.1 for omeprazole -d_3 (IS) in MRM positive mode.			
Sample volume	50 µL			
Regression	Linear			
Weighting factor	$1/x^2$			
Dynamic range	1.00 – 1000 ng/mL			
QC concentrations	1.00 ng/mL (LLOQ), 3.00 ng/mL, 300 ng/mL, 750 ng/mL, and 7500 ng/mL (Dilution QC)			
Analytes	Omeprazole			
Internal standard	Omeprazole -d_3			
Coefficient of Determination	$R^2 \geq 0.9994$			
Lower limit of quantitation (LLOQ)	1.00 ng/mL			
QC Level	**LLOQ (1.00 ng/mL)**	**Low (3.00 ng/mL)**	**Mid (300 ng/mL)**	**High (750 ng/mL)**
QC Intra-run precision (%CV)	13.3	5.9	1.3	2.8
QC Intra-run accuracy (%Bias)	4.0	-9.0	-1.7	-7.6
2% Hemolyzed QC precision range (%CV)[1]	2.4 to 3.3			
2% Hemolyzed QC accuracy range (%Bias)[1]	2.8 to 2.8			
Average recovery of the Analyte (%)[1]	102.7			
Average recovery of the IS (%)	Per BIO-201 guidelines, if a stable isotope labeled IS was used, the recovery established for the unlabeled analyte will suffice and the recovery for the stable isotope labeled IS will not be required.			
QC sample bench-top stability[1]	6.5 hours at room temperature			
Stock solution stability	99 days at -20 °C[2] 6 hours at room temperature under white light[1]			
Processed sample stability[1]	79 hours at room temperature			
Reinjection reproducibility[1]	Not performed: Processed sample stability was adequate as per protocol.			
QC sample freeze/thaw stability	3 freeze/thaw cycles at both -20 °C[3] and -70 °C[1]			
QC sample long-term storage stability[3]	82 days at -20 °C and -70 °C			
Dilution integrity	7500 ng/mL diluted 10-fold			
Matrix Effect[1]	IS-normalized Matrix factor = 1.12 ± 0.08 at 3.00 ng/mL with %CV = 7.1% IS-normalized Matrix factor = 0.99 ± 0.04 at 750 ng/mL with %CV = 4.0%			
Blank Selectivity[14]	The blank selectivity samples were within acceptance criteria (all 6 blank samples at the retention time of the analytes were within ≤ 20% of the mean peak area of the analytes of the 6 matrix LLOQ samples and all 6 blank samples at the retention time of the IS were within ≤ 5% of the mean peak area of the IS of the matrix LLOQ samples).			
Maximum Batch Size	215 samples			
Carry-over Evaluation[4]	The double blank sample evaluated for carryover met the acceptance criteria: analyte peak areas were <20.0% of the LLOQ for omeprazole and IS peak areas were <5.0% of the IS peak area of the accepted calibration standards and QC samples for the IS.			
Interference from Analyte on IS[4]	There was no interference detected from the analyte on the internal standard.			
Whole Blood Stability[5]	2 hours at room temperature and in an ice-water bath (0-4 °C)			

Source: Table from Validation Report: 1629-R9347
Abbreviations: CV, coefficient of variation; K2EDTA, dipotassium ethylenediaminetetraacetic acid; LC-MS/MS, Liquid chromatography–mass spectrometry; MRM, multiple reaction monitoring; QC, quality control

Analysis of Study Samples

A total of 4176 study samples were analyzed. A total of 262 samples were selected for the incurred sample reproducibility test to demonstrate that results obtained from study sample analysis are reproducible. Results from the ISR analysis indicated that 97 % of the reanalyzed samples met the criteria of assay reproducibility (minimum requirement 67 %). The within-run and between-run accuracy and precision of calibration and quality control samples during the from the in-study analytical runs were acceptable (% bias less than 10 % and % CV less than 5 %).

Pharmacokinetic and BE Analysis Results

The mean BE analysis and PK parameters under fasting conditions are summarized in Table 5 and Table 6, respectively. The plots of the mean plasma levels over the sampling period are presented in Figure 3 and Figure 5.

The BE analysis conducted by the reviewer to verify the Applicant's analysis is summarized in Table 19.

Reviewer's comments: The reviewer repeated the BE analysis from adpc.xpt, the dataset that contains concentration data. The repeat analysis using Phoenix 64 (version 3) confirmed the Applicant's conclusion that the pharmacokinetics of omeprazole and sodium bicarbonate for oral suspension (RM-02, Test Formulation) 40 mg and Zegerid (40 mg/1680 mg, Reference #1) were similar. C_{max}, AUC0-inf and AUC0-t for the Applicant's product relative to Zegerid was within the criterion for bioequivalence (90% CIs for the geometric mean ratios were within the 0.80 to 1.25).

As expected, omeprazole and sodium bicarbonate for oral suspension (RM-02, Test Formulation) had higher mean C_{max} values (90 % CI for GMRs ranged from 146 – 174 %) compared to Omeprazole DR capsules (Treatment C). However, the upper bound (174%) of the 90% CI for the GMR of C_{max} for omeprazole and sodium bicarbonate for oral suspension (RM-02, Treatment A) relative to Omeprazole DR capsules (Treatment C) was lower than the upper bound (191%) of 90% CI of the ratio of Zegerid (Treatment B) relative to Omeprazole DR capsules (Treatment C).

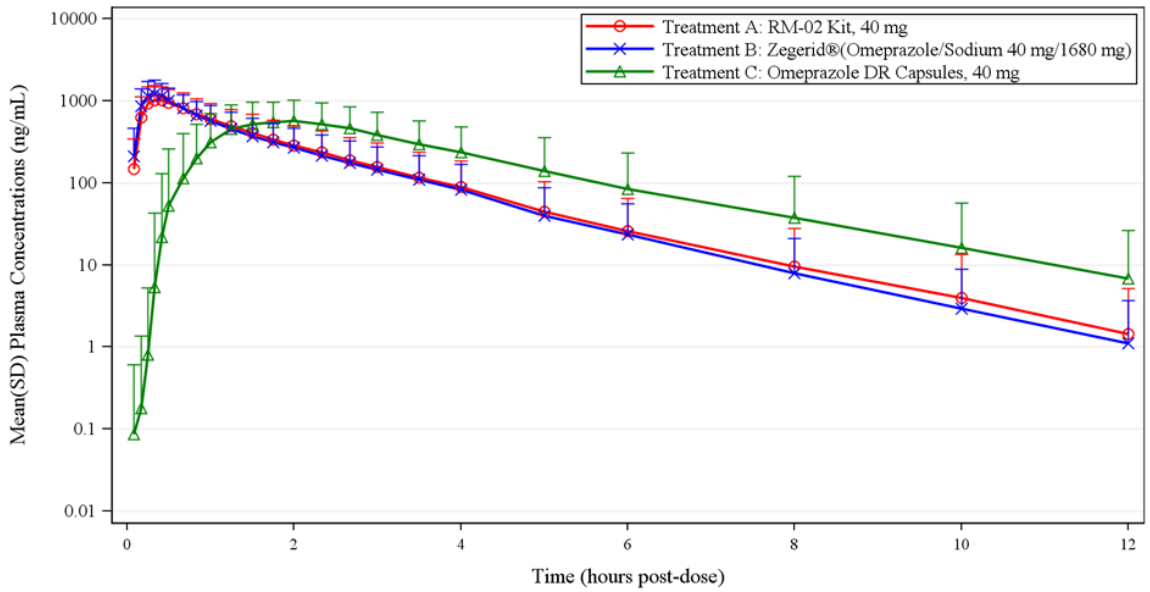
Table 19. Summary of Reviewer's Statistical Analysis of Bioequivalence Assessment (Study OME-RM02-001)

				90% Geometric CI of GMR	
Test Arm	**Treatment Comparison**	**Parameter**	**GMR**	**Lower**	**Upper**
Treatment A: Omeprazole and sodium bicarbonate for oral suspension (RM-02), 40 mg (test)	Treatment A – Treatment B (Zegerid – powder for oral suspension)	AUC_{0-t} (h*ng/mL)	100.50	95.67	105.56
		C_{max} (ng/mL)	90.91	83.46	99.04
	Treatment A – Treatment C	AUC_{0-t} (h*ng/mL)	93.67	89.13	98.46

Test Arm	Treatment Comparison	Parameter	GMR	90% Geometric CI of GMR Lower	Upper
Treatment B (Zegerid – powder for oral suspension)	Treatment C (Prilosec – delayed release capsules)	C_{max} (ng/mL)	159.35	146.13	173.78
		AUC_{0-t} (h*ng/mL)	93.21	88.74	97.91
		C_{max} (ng/mL)	175.28	160.91	190.94

Source: Reviewer generated table
Abbreviations: AUC_{0-t}, area under the plasma concentration to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio

Figure 5. Mean (SD) Omeprazole Plasma Concentrations (ng/mL) Versus Time (Semi Logarithmic Scale) – PK Population



Source: The Applicant's submitted figure, CSR, p. 57/76.
Abbreviations: DR, delayed-release; PK, pharmacokinetic

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Division Director DGIEP	Jessica Lee, MD, MMSc	OII / DG	Authored Section: 14 Approved Sections: All	**Select one:** _X_ Authored _X_ Approved
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