CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214278Orig1s000

MULTI-DISCIPLINE REVIEW

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

NDA Multi-Disciplinary Review and Evaluation

Application Type	Original NDA
Application Number	NDA 214278
Priority or Standard	Standard
Submit Date(s)	December 20, 2019
Received Date(s)	December 20, 2019
PDUFA Goal Date	October 20, 2020
Division/Office	Division of Nonprescription Drugs I, Office of Nonprescription Drugs
Review Completion Date	October 20, 2020
Established/Proper Name	Esomeprazole
(Proposed) Trade Name	N/A
Pharmacologic Class	Proton Pump Inhibitor
Applicant	Dexcel Pharma Technologies Limited
Dosage form	Delayed-release orally disintegrating tablet, 20 mg
Applicant Proposed Dosing Regimen	One 20 mg tablet per day for a 14-day course of treatment
Applicant Proposed Indication(s)/ Population(s)	Treatment of frequent heartburn (occurs 2 or more days a week) in adults (18 years of age and older)
Recommendation on Regulatory Action	Approval
Recommended Dosing Regimen	Same as proposed

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Glossary

ADR	adverse drug reaction
AE	adverse event
AIN	acute interstitial nephropathy
ANDA	Abbreviated New Drug Application
AUC	area under the concentration curve
AV	acceptance value
BA	bioavailability
BE	bioequivalence
CDAD	*Clostridium difficile*-associated diarrhea
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CgA	chromogranin A
CHMP	Committee for Medical Products for Human Use of the European Medicines Agency
CI	confidence interval
C_{max}	maximum concentration
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRT	clinical review template
CSR	clinical study report
CV	coefficient of variation
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DFL	Drug Facts label
DIIP	Division of Inflammation and Immune Pharmacology
DMEPA	Division of Medication Error Prevention and Analysis
DMF	Drug Master File
DNPD1	Division of Nonprescription Drugs 1
DR	delayed-release
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EMA	European Medicines Agency
FACE	Fellow of the American College of Endocrinology
FAERS	FDA Adverse Event Reporting System
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
FPI	Full Prescribing Information
GCP	good clinical practice
GERD	gastroesophageal reflux disease
GMR	geometric mean ratio
GRAS	generally recognized as safe
HR	hour
ICH	International Conference on Harmonisation
ID	identification or identification number

IND	Investigational New Drug
IR	Information request
ISS	Integrated Summary of Safety
JECFA	Joint Food and Agriculture Organization of the United Nations and World Health Organization Expert Committee on Food Additives
K_{el}	elimination rate constant
LC	liquid chromatography
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
MS	mass spectrometry
N/A	not applicable
NDA	New Drug Application
NISS	Newly Identified Safety Signal
OCP	Office of Clinical Pharmacology
ODT	orally disintegrating tablet
OND	Office of New Drugs
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTC	over-the-counter
PD	pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PeRC	Pediatric Review Committee
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	proton pump inhibitor
PREA	Pediatric Research Equity Act
PT	Medical Dictionary for Regulatory Activities Preferred Term
Q	calendar quarter
QC	quality control
REMS	risk evaluation and mitigation strategy
Rx	by prescription only
SD	standard deviation
SAE	serious adverse event
SOC	Medical Dictionary for Regulatory Activities System Organ Class
SOP	standard operating procedure
SSID	Safety Signal Identification number
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TL	team leader
TSI	Tracked Safety Issue
V/V	volume per volume
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Dexcel Pharma Technologies, Ltd. (Dexcel) submitted an original New Drug Application (NDA) 214278 under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act on December 20, 2019. The Applicant proposes to market the proton pump inhibitor, esomeprazole magnesium trihydrate, 22.3 mg (esomeprazole, 20 mg, per the United States Pharmacopeia (USP) Salt Policy) delayed-release, orally disintegrating tablet for the nonprescription treatment of frequent heartburn (occurs 2 or more days a week) in adults 18 years and older. The proposed dosage is 20 mg once daily for 14 days.

Esomeprazole delayed-release (DR), orally disintegrating tablet (ODT) is to be placed on the tongue, disintegrated, and may be swallowed with or without water. In addition, the esomeprazole delayed-release orally disintegrating tablet may be swallowed whole with water. The product is not to be crushed or chewed.

This drug product would be a new dosage form for nonprescription esomeprazole as the other nonprescription esomeprazole dosage forms include DR capsules (NDA 204655) and DR tablets (NDA 207920). The proposed listed drug is Nexium 24HR (esomeprazole magnesium) delayed-release capsule (NDA 204655), hereafter referred to as Nexium 24HR. The proposed drug product does not have a proprietary name. Instead, the Applicant plans to market the proposed drug product using the established name of the active ingredient (esomeprazole, 20 mg).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant proposed to rely on the FDA's previous finding of safety and efficacy of Nexium 24HR (esomeprazole magnesium) delayed-release capsule, a listed drug (NDA 204655). The proposed indication and the dosage regimen are the same as the listed drug, Nexium 24HR delayed-release capsule.

To establish a scientific bridge to justify such reliance, the Applicant conducted a single-dose relative bioavailability (BA) study (Study 11742615) to compare the proposed product to the listed drug (Nexium 24HR delayed-release capsule). In the relative BA study, the systemic exposure to esomeprazole after single-dose administration of esomeprazole DR ODT, 20 mg and Nexium 24HR, 20 mg met the bioequivalence criteria. Of note, in the relative BA study, esomeprazole DR ODT was administered by placing on the tongue, and swallowing with or without water; or swallowing whole with water. Esomeprazole DR ODT resulted in equivalent bioavailability to that of Nexium 24HR capsule regardless of administration method, which supports the labeling of all three administration methods for the proposed esomeprazole DR ODT. No other clinical safety and efficacy trials were conducted with the proposed esomeprazole DR ODT.

As such the reliance on Nexium 24HR capsules for efficacy is justified by comparable

bioavailability between the proposed esomeprazole DR ODT and Nexium 24HR capsule. In conclusion, the proposed esomeprazole DR ODT is expected to be as efficacious as Nexium 24HR capsules for the treatment of frequent heartburn for the nonprescription use.

1.3. Benefit-Risk Assessment

Dimension	Evidence and Uncertainties Conclusions and Reasons
Current Treatment Options	Esomeprazole is a proton pump inhibitor (PPI) currently used for the treatment of acid-related gastrointestinal disorders. The active ingredient, esomeprazole, was approved as a prescription product in the United States (U.S.) in 2001 and subsequently, as a nonprescription product in 2014 (NDA 204655, Nexium 24HR capsule). Esomeprazole delayed-release, 20 mg capsules and tablets are currently marketed for the nonprescription indication: treatment of frequent heartburn (occurring two or more days a week) in adults 18 years of age and older, used once a day for 14 days. There are several FDA-approved treatment options, including other proton pump inhibitors in the ODT formulation (lansoprazole and omeprazole), available for frequent heartburn in the nonprescription setting. The proposed esomeprazole delayed-release, orally integrating tablet is a new dosage form for nonprescription esomeprazole.
Benefit-Risk	The benefit-risk profile for esomeprazole delayed-release, orally integrating tablet is determined to be similar to Nexium 24HR capsules, based on demonstration of comparable bioavailability (BA) between the two products. No new safety concerns were identified in the relative BA study and a food-effect study conducted with esomeprazole delayed-release, orally integrating tablet. In the bioavailability studies, more subjects experienced dysgeusia when they took esomeprazole delayed-release, orally disintegrating tablet without water, compared to subjects who took the listed drug. Dysgeusia is apparently associated with the administration method of placing the proposed ODT on the tongue. The oral safety was also assessed in the relative BA study and a food-effect study and deemed acceptable. Safety issues are reflected through consumer language on the nonprescription Drug Facts label (DFL) for Nexium 24HR, with the labeled duration and frequency of use factoring into the relevance of safety language. Proposed labeling for esomeprazole delayed-release, orally integrating tablet is consistent with current safety language of the listed drug (Nexium 24HR capsule) and is appropriate. As such, the benefit-risk profile for esomeprazole delayed-release, orally integrating tablet is favorable to support approval.

Dimension	Evidence and Uncertainties Conclusions and Reasons
Risk and Risk Management	Of note, prescription (Rx) labeling for Nexium includes a warning for acute interstitial nephritis (AIN) observed in patients taking PPIs (label update December 2014). Evidence of kidney injury associated with PPI and tracked as a safety issue (Newly Identified Safety Signal (NISS) 392, Safety Signal Identification Number (SSID) 1001781, Tracked Safety Initiative (TSI) 1781) resulted in a May 14, 2020 recommendation for a prescription PPI class labeling revision from AIN to tubulointerstitial nephritis having both acute and chronic phases. The applicability of the Rx PPI class warning for kidney injury (tubulointersitial nephritis) to nonprescription PPI labeling was commented on in the TSI integrated review.[1] The TSI review noted that the weight of currently available evidence does not yet support the inclusion of kidney injury in the nonprescription PPI labeling, particularly given the prolonged exposures (2.7-13.9 years) noted for the cases of kidney injury compared to the labeled short duration of use per treatment course (14 days) in the nonprescription setting. The nonprescription PPI labeling states "Do not take for more than 14 days or more often than every 4 months unless directed by a doctor". This safety signal remains under surveillance and review by the Proton Pump Inhibitors Safety Issues Working Group (PPISIWG); the signatory (Dr. Karen Minerve Murry) for this application does not recommend nonprescription class labeling at this time, but a labeling change may be considered as more data emerge over time and are reviewed by the PPISIWG.

[1] NISS Integrated Review Memorandum, April 30, 2020

1.4. Patient Experience Data

No patient experience data were submitted.

2 Therapeutic Context

2.1.1. Analysis of Condition

Esomeprazole is a proton pump inhibitor (PPI) currently used for the treatment of acid-related gastrointestinal disorders. Esomeprazole was developed as the S-isomer of omeprazole in an attempt to improve its pharmacokinetic properties.[2,3] The active moiety, esomeprazole, was approved as a prescription product in the United States in 2001 and subsequently, as a nonprescription product in 2014 (NDA 204655, Nexium 24HR).

Esomeprazole delayed-release, 20 mg capsules and tablets are currently marketed for the nonprescription indication, i.e., treatment of frequent heartburn (occurring two or more days a week) in adults 18 years of age and older, used once a day for 14 days. This treatment course may be repeated every four months if necessary, for a maximum of three courses in one year. The product is to be taken in the morning before eating.

As a prescription product, esomeprazole is available in dosage strengths 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg as delayed-release oral suspension; 20 mg and 40 mg delayed-release capsule; and IV formulations. Adult prescription dosing is indicated for treatment of gastroesophageal reflux disease (GERD); risk reduction of gastric ulcer associated with use of nonsteroidal anti-inflammatory drugs; *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence; and pathological hypersecretory conditions, including Zollinger-Ellison syndrome. It is also approved for infants and children in the short-term treatment of GERD.[4]

2.1.2. Analysis of Current Treatment Options for Proposed Indications

Approved nonprescription PPIs for the treatment of frequent heartburn (occurring two or more times a week) are shown in Table 1. The table does not include generics.

[2]Hatlebakk JG. Review article: gastric acidity – comparison of esomeprazole with other proton pump inhibitors. Aliment Pharmacol Ther. 2003;17(Suppl 1):10–15.
[3]Kalaitzakis E, Björnsson E. A review of esomeprazole in the treatment of gastroesophageal reflux disease (GERD). Ther Clin Risk Manag. 2007;3(4):653-663.
[4] https://www.accessdata fda.gov/drugsatfda_docs/label/2014/022101s014021957s017021153s050lbl.pdf

Table 1. Approved Nonprescription Proton Pump Inhibitor Products

NDA	Applicant	Proprietary Name	Established Name	Dosage	Year Approved
021229	Astra Zeneca	Prilosec OTC	omeprazole (delayed-release, tablet)	20 mg	2003
022032	Dexcel	none	omeprazole (delayed-release, tablet)	20 mg	2007
022281	MSD Consumer	Zegerid OTC	omeprazole and sodium bicarbonate (capsule)	20 mg	2009
022237	Novartis	Prevacid 24HR	lansoprazole (capsule)	15 mg	2009
022283	MSD Consumer	Zegerid OTC	omeprazole and sodium bicarbonate (for oral suspension)	20 mg	2013
204655	Astra Zeneca	Nexium 24HR	esomeprazole (delayed-release, capsule)	20 mg	2014
207920	Pfizer and Astra Zeneca	Nexium 24HR	esomeprazole (delayed-release, tablet)	20 mg	2015
208025	Dexcel	none	lansoprazole (delayed-release, orally disintegrating tablet)	15 mg	2016
209400	Dexcel	none	omeprazole (delayed-release, orally disintegrating tablet)	20 mg	2017

Source: Table by clinical reviewer from content at https://www.accessdata.fda.gov/scripts/cder/daf/

There are other nonprescription products approved for acid-related gastrointestinal disorders (acute relief and prevention of heartburn). Examples of these products include H_2-receptor antagonists (cimetidine, famotidine, nizatidine) and antacids (aluminum and/or magnesium hydroxide, calcium bicarbonate, sodium bicarbonate).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

3.1.1. Availability of Proposed Active Ingredient in the United States

There are several esomeprazole products available for prescription use at dosages ranging from 2.5 mg to 40 mg. The active ingredient esomeprazole is also available for the nonprescription use as tablet and capsule formulations at 20 mg.

3.1.2. Important Safety Issues with Consideration to Related Drugs

PPIs are widely used and have been found to be generally safe and well-tolerated. The most common adverse effects associated with PPIs in adults are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth. The current prescription Nexium labeling (2018)[5] includes the following warnings and precautions:

- Gastric Malignancy: In adults, symptomatic response does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing.
- Acute Interstitial Nephritis: Observed in patients taking PPIs.
- *Clostridium difficile*-Associated Diarrhea: PPI therapy may be associated with increased risk.
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine.
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue Nexium and refer to specialist for evaluation.
- Fundic Gland Polyps: Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy.
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin.
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs.
- Interaction with Clopidogrel: Avoid concomitant use of Nexium.
- Interaction with St. John's Wort or Rifampin: Avoid concomitant use of Nexium.
- Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increased chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors; temporarily stop Nexium at least 14 days before assessing CgA levels.
- Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider temporary withdrawal of Nexium.

These important safety issues are generally reflected through consumer language on the nonprescription Drug Facts label (DFL) for Nexium 24HR, with the labeled duration and frequency of use factoring into the relevance of safety language intended to support safe use in the nonprescription setting. Table 2 illustrates Applicant-proposed safety labeling consistent with current nonprescription PPI warnings.

[5] https://www.accessdata fda.gov/drugsatfda_docs/label/2018/021153s053,022101s017,021957s020lbl.pdf

Table 2. Applicant Draft Label Warnings with Reference to Nonprescription Proton Pump Inhibitor Labeling

Warnings **Allergy alert**: Do not use if you are allergic to esomeprazole	Nexium® 24HR, Capsules, Label April 2019
Do not use if you have: ▪ trouble or pain swallowing food, vomiting with blood, or bloody or black stools ▪ heartburn with **lightheadedness, sweating or dizziness** ▪ chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness ▪ frequent **chest pain** These may be signs of a serious condition. See your doctor.	Nexium® 24HR, Capsules, Label April 2019
Ask a doctor before use if you have ▪ had heartburn over 3 months. This may be a sign of a more serious condition. ▪ frequent wheezing, particularly with heartburn ▪ unexplained weight loss ▪ nausea or vomiting ▪ stomach pain	Nexium® 24HR, Capsules, Label April 2019
Ask a doctor or pharmacist before use if you are ▪ taking a prescription drug. Acid reducers may interact with certain prescription drugs.	Nexium® 24HR, Capsules, Label April 2019
Stop use and ask a doctor if ▪ your heartburn continues or worsens ▪ you need to take this product for more than 14 days ▪ you need to take more than 1 course of treatment every 4 months ▪ you get diarrhea ▪ you develop a rash or joint pain	Nexium® 24HR, Label Capsules, April 2019
If pregnant or breast-feeding, ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222).	Nexium® 24HR, Capsules, Label April 2019

Source: Excerpted from NDA 214278, Module 1.14.1.2, Annotated Draft Labeling Text, page 1

3.2. Summary of Presubmission/Submission Regulatory Activity

For this application, the Applicant proposed to rely on the FDA's previous findings of safety and efficacy of the listed drug Nexium 24HR for nonprescription use. To establish a scientific bridge to justify such reliance, the Applicant conducted a relative bioavailability study to compare the proposed product to the listed drug (Nexium 24HR). In addition, a food-effect study for the proposed ODT product was conducted to support the labeling. No other clinical safety and efficacy trials were conducted for the proposed product. The oral safety for the administration method, i.e., dissolve on the tongue, was conducted during the BA/BE studies.

In addition, the Applicant refers to two clinical trials reported in the scientific literature supporting approval of the safety and efficacy of esomeprazole 20 mg DR in the nonprescription setting; other published literature; and adverse event (AE) reports identified in postmarketing databases (FDA Adverse Event Reporting System (FAERS), World Health Organization drug alert) over a time period of collection beginning in 2014.

The details of the Applicant's plan were discussed at a pre-IND meeting held May 23, 2016 and a pre-NDA meeting held on October 31, 2019. Discussions between the Applicant and FDA included the following topics:

- Two pharmacokinetics studies – one pivotal relative bioavailability and one food-effect

study with adequate data collection to support safety
- include a rationale supporting the safety of using the drug over a 14-day treatment period
- support repeated use of the ODT formulation for the duration of treatment (14 days) in the nonprescription setting (e.g., oropharyngeal assessments). Methodology of the completed oral safety evaluations and the safety results data will be reviewed as part of the formal NDA review process.
- include an Integrated Summary of Safety (ISS) with analysis of safety from the development program, including adverse events stemming from oral exposure, serious adverse events, deaths, and events resulting in discontinuation. Assuming it meets criteria outlined in the guidance, ISS content may be submitted in Module 2.7.4 only.
- provide a rationale for how the results of BA studies conducted outside the U.S. are generalizable to the U.S. population
- conduct a comparative food-effect study to assess the extent of the food effect on the product and consider impact for proposed labeling (with or without water statement)

Clinical reviewer comment: The Applicant has addressed these issues in the NDA.

- Analysis of postmarketing safety of PPIs for nonprescription use
  - provide analysis and discussion by formulation and strength for postmarketing database search results. Agreed with plan for no data from National Poison Data System (NPDS) database.
  - include the following topics of interest:
    - acute and chronic kidney injury
    - cardiovascular events
    - hypocalcemia
    - acute generalized exanthematous pustulosis (AGEP)
    - acute and chronic pancreatitis
    - hepatic encephalopathy and spontaneous bacterial peritonitis
    - all-cause mortality
    - misuse (use greater than 14 days or three 14-day courses in one year)
  - include a comprehensive literature review that contains a synthesized discussion of the findings with summary conclusions
  - assess and discuss findings relevant to differences in any part of the safety profile between immediate- and delayed-release formulations
  - include data up until at least the NDA submission date in the 4-month (120-day) safety update

Clinical reviewer comment: The Applicant has addressed these issues in the NDA. Data for the 120-day safety update were submitted April 17, 2020.

- No other clinical or nonclinical studies required
  - no additional safety studies required if all ingredients adequately qualified and no safety concerns arise from the oropharyngeal examinations

- provide adequate justification for each proposed excipient. Ascorbic acid proposed as a "Generally Recognized as Safe" (GRAS) substance, inactive ingredient, will be assessed for safety as part of the NDA review
- recommend inclusion of proposal of disintegration test and acceptance criterion in the NDA

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

4.1. Office of Scientific Investigations (OSI)

Not applicable.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) review concluded that the quality aspects of the drug substance, drug product, biopharmaceutics, process, and facility are adequate; OPQ recommends approval. As of September 4, 2020, the facilities remained adequate. Refer to the Office of Pharmaceutical Quality review for more details (DARRTS Reference ID: 4664136).

Esomeprazole delayed-release orally disintegrating tablets, 20 mg, are round bluish mottled uncoated tablets, debossed "20" on one side. The orally disintegrating tablet (ODT) is comprised of coated pellets containing the active substance, esomeprazole magnesium trihydrate, mixed with excipients to form a tablet that disintegrates when placed on the tongue. The formulation contains a single active ingredient, esomeprazole 20 mg (esomeprazole magnesium trihydrate 22.27 mg).

The tablets are packaged in 7-count aluminum (b) (4) blisters. Each pack contains two blisters (each blister contains 7 tablets with a total of 14 tablets per pack) for one 14-day course of treatment. Esomeprazole delayed-release orally disintegrating tablets will be available in 14, 28, and 42 count blister cartons, for one, two and three courses of treatment.

The OPQ review noted that no novel excipients are used in the manufacture of or are present in the drug product, and (b) (4) is the only ingredient that is not included in the FDA inactive ingredients database (IID) or in approved products; however, each of its component is present in the IID and were found acceptable. The drug product formulation also contains two other noncompendial excipients: (b) (4) and the (b) (4) berry flavor mixture. Quantitative composition for (b) (4) is included in the application and manufacturing detail is referred to DMF (b) (4). Similarly, quantitative information for the (b) (4) berry flavor mixture is provided in the application and manufacturing detail is referred to DMF (b) (4). Both (b) (4) and the (b) (4) berry flavor mixture information were found acceptable by the Drug Product reviewers.

The OPQ review also noted that the impurities were below the specified reporting threshold and hold up well over 12 months at conditions 25°C/60% humidity. As such the impurity profile

appears to be unchanged on storage under normal conditions, 25°C/60% humidity. There were no major degradants reported.

Per the Biopharmaceutics review, the in vitro alcohol-induced dose dumping study showed premature release of the drug at alcohol concentrations ≥ 40% volume per volume (v/v) but not at 5%, 10%, and 20%.

Because esomeprazole is an acid-labile drug, a premature release of esomeprazole from the delayed-release formulation in vivo due to concomitant alcohol consumption may lead to degradation of esomeprazole in the stomach and may compromise the efficacy of the product. The Applicant has proposed to include a statement "do not take this medicine with alcohol" in the label and did not conduct an in vivo alcohol-induced dose dumping study to evaluate the magnitude of effects of alcohol consumption on the pharmacokinetics (PK). The clinical pharmacology reviewers found the proposal acceptable.

The disintegration specifications, which are critical quality attributes that differentiate the proposed DR ODT formulation from the listed drug, were set with the same acceptance criteria of (b) (4) seconds at both release and stability.

The drug product is granted a 24-month shelf life when stored at controlled room temperature.

5 Nonclinical Pharmacology and Toxicology

The nonclinical review concluded that adequate safety justification has been provided for the active ingredient, excipients, and impurities in the proposed drug product from a nonclinical perspective. The nonclinical reviewers recommend approval. Refer to the pharmacology and toxicology review for more details (DARRTS Reference ID: 4655645).

No new nonclinical toxicology studies were conducted for the proposed esomeprazole DR ODT. The Applicant proposed to rely the FDA's finding of safety for the listed drug, Nexium 24HR. As the ODT showed equivalent systemic exposure to Nexium 24HR, the reliance of nonclinical safety of esomeprazole on Nexium 24HR is justified.

The nonclinical reviewers also noted that the proposed ODT formulation, except for the (b) (4) berry flavor mixture, does not contain any novel excipients and the amounts of the proposed excipients are within the amounts in other FDA-approved oral (or intraoral) products. The nonclinical reviewers found this adequate. In addition, each of the components of the (b) (4) berry flavor mixture is adequately supported by the GRAS designations in the CFR or by Joint Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) determinations. The natural and artificial flavoring ingredients in the Applicant's proposed (b) (4) berry flavor mixture (b) (4) are specified in Drug Master File (DMF) (b) (4) for which a Letter of Authorization was provided.

In addition, there are no concerns with the compendial control of drug product impurities per the OPQ review; the impurity levels are within reporting threshold limits, and the proposed drug product has a stable impurity profile without any major degradants reported. Therefore, there are no remaining nonclinical issues for the impurities.

6 Clinical Pharmacology

6.1. Executive Summary

In this submission, the Applicant proposed a new delayed-release orally disintegrating tablet (ODT) for 20 mg esomeprazole for nonprescription use in the treatment of frequent heartburn in adults 18 years of age and older. The proposed dosing regimen is one 20 mg tablet per day for a 14-day course of treatment.

For the efficacy and safety of the proposed ODT formulation, the Applicant proposed to rely on the FDA's previous findings for efficacy and safety of the listed drug (LD) - Nexium 24HR capsule (NDA 204655; esomeprazole magnesium delayed-release capsule, 20 mg of esomeprazole). The proposed indication for the proposed esomeprazole ODT 20 mg nonprescription product is the same as that approved for Nexium 24HR. The proposed dosing method is to disintegrate the ODT on the tongue and swallow with water or without water. In addition, swallowing the whole tablet is also proposed.

To establish the scientific bridge to Nexium 24HR, the Applicant conducted a pivotal relative bioavailability (BA) study under fasting condition in healthy male and female subjects (Study# 190030). The Applicant also evaluated the effect of food on the PK of esomeprazole following the administration of esomeprazole DR ODT in fed and fasted state. No other clinical trials for efficacy and safety were conducted. The Applicant has also conducted in vitro comparative dissolution studies and evaluated alcohol-induced dose dumping using in vitro methods. For the review of the comparative dissolution and alcohol-induced dose dumping studies, please refer to the review by the biopharmaceutics review team.

6.1.1. Recommendation

The Division of Inflammation and Immune Pharmacology (DIIP) in the Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint and concluded that the Applicant adequately established the scientific bridge between the proposed esomeprazole DR ODT and Nexium 24HR for the reliance on FDA's previous findings of safety and efficacy for Nexium 24HR.

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 (Memo dated 3rd February 2020 by Folaremi Adeyemo, Ref ID:4555575 in DARRTS).

The proposed labeling for swallowing the disintegrated tablet with or without water, or swallowing the tablet whole with water is acceptable. In addition, the Applicant proposal to include "do not take this medicine with alcohol" based on the in vitro alcohol-induced dose dumping study is acceptable. Concomitant food intake with the ODT significantly reduced the systemic exposure to esomeprazole. The mean maximum concentration (C_{max}) and area under the concentration curve (AUC) for esomeprazole after the ODT was administered under fed condition were 25% and 47% of those after the ODT was administered under fasted condition. The proposed dosing instruction of "take 1 tablet before eating in the morning" is acceptable given the significant food effects, and is consistent with the labeling of the listed drug.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Relative Bioavailability Between Esomeprazole Delayed-Release Orally Disintegrating Tablet and Nexium 24HR

The Applicant conducted a single-center, randomized, single-dose, open-label, 4-way crossover bioequivalence study (Study 190030) to evaluate the relative BA (fasted state) between esomeprazole DR ODT (20 mg) placed on the tongue and administered without or with water, or swallowed whole with water versus Nexium 24HR (reference product).

Results from Study 190030 indicated that esomeprazole ODT provides comparable bioavailability to Nexium 24HR capsule under fasting conditions under all three modes of dosing (placed on the tongue and administered without or with water, or swallowed whole with water). The 90% CIs for the ratio of the geometric means of AUC_{0-t}, AUC_{0-inf} and C_{max} were within the bioequivalence acceptance criteria of 80-125% (Table 3).

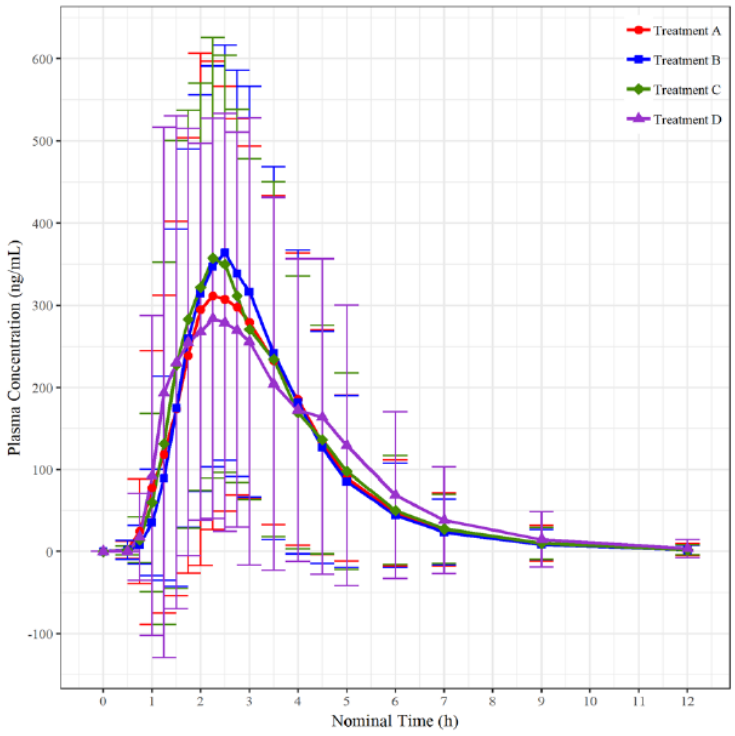
Table 3. Summary of Bioequivalence Assessment of Esomeprazole Delayed-Release, Orally Disintegrating Tablet 20 mg Compared to Nexium 24HR Capsule 20 mg

Dosing Method ODT	PK Parameter	Treatment Comparisons	90% Geometric CI			Intra-Subject CV (%)	Inter-Subject CV (%)
			Ratio	Lower (%)	Upper (%)		
ODT placed on tongue and swallowed without water	AUC_{0-t}	Test (A)-Reference (D)	93.68	88.08	99.63	16.85	84.47
	AUC_{0-inf}	Test (A)-Reference (D)	93.63	88.16	99.43	16.44	84.07
	C_{max}	Test (A)-Reference (D)	90.3	82.56	98.86	24.83	59.63
ODT placed on tongue and swallowed with water	AUC_{0-t}	Test (B)-Reference (D)	104.48	99.08	110.18	14.50	79.92
	AUC_{0-inf}	Test (B)-Reference (D)	104.16	98.81	109.79	14.39	79.38
	C_{max}	Test (B)-Reference (D)	107.73	98.18	118.22	25.64	49.78
ODT swallowed whole with water	AUC_{0-t}	Test (C)-Reference (D)	102.50	97.21	108.07	14.81	81.97
	AUC_{0-inf}	Test (C)-Reference (D)	102.16	96.93	107.67	14.69	81.65
	C_{max}	Test (C)-Reference (D)	104.16	95.06	114.13	25.82	49.91
Source: Study Report: Study 190030, Table 11.4.1-3 to Table 11.4.1-5							

Test (A): 1 x 20 mg esomeprazole DR ODT placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed without water.
Test (B): 1 x 20 mg esomeprazole DR ODT placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed with water.
Test (C): 1 x 20 mg esomeprazole DR ODT swallowed with water.
Reference (D): 1 x 20 mg Nexium 24HR (Pfizer, USA) DR capsule swallowed with water.
Abbreviations: AUC = area under the concentration curve; CI = confidence interval; C_{max} = maximum concentration; CV = coefficient of variation; ODT = orally disintegrating tablet; PK = pharmacokinetic

Figure 1 illustrates the plasma concentration-time profile for esomeprazole. It was noted that there were minor differences in the performance of the esomeprazole ODT among the three modes of dosing (placed on the tongue and swallowed without or with water, or swallowed whole with water) as C_{max} and AUC tended to be lower when the product was swallowed without water after placing on tongue (Test A) compared to other dosing methods (Test B and C), although all three dosing methods result in comparable bioavailability relative to the reference product (Nexium 24HR capsule). The clinical pharmacology reviewer's independent analysis of the Applicant's data confirmed these results and supported the Applicant's conclusion.

Figure 1. Mean (±SD) Concentration-Time Profile for Esomeprazole Following Administration of Esomeprazole Delayed-Release, Orally Disintegrating Tablet 20 mg and Nexium 24HR 20 mg Capsule



Test (A): Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed without water.
Test (B): Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed with water.
Test (C): Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet swallowed with water.
Reference (D): Pfizer, USA (Nexium® 24HR), Esomeprazole 1 x 20 mg delayed-release capsule swallowed with water.

Data Source: Figure 11.4.1-1 from Table 11.4.1-4 from clinical study report for Study 190030

6.2.2. Food-Effect Study (Study 190031)

The Applicant evaluated the effects of food on the performance of the esomeprazole DR ODT in a randomized, single-dose, open-label, 2-way crossover bioavailability study aimed to assess the effect of food on the rate (C_{max}) and extent (AUC) of absorption of esomeprazole DR ODT (20 mg) following a 20 mg dose in 18 healthy subjects under fed and fasting conditions.

The following dosage conditions were used in the study:

- Treatment A: A single 20 mg esomeprazole DR ODT placed on the tongue and allowed to disintegrate until the particles could be swallowed, and then swallowed without water under fed conditions.
- Treatment B: A single 20 mg esomeprazole DR ODT placed on the tongue and allowed to disintegrate until the particles could be swallowed, and then swallowed without water under fasting conditions.

The median time to maximum concentration (T_{max}) was delayed under fed condition (median T_{max} ~ 4.5 hr) compared to fasted state (median T_{max} ~ 1.7 hr). The mean C_{max} and AUC for esomeprazole after the ODT was administered under fed condition were 25% and 47% of those after the ODT was administered under fasted condition, respectively. PK parameters and statistical analyses of food effect on PK are summarized in Table 4 and Table 5. The results of the food-effect study indicated that the rate and extent of absorption were decreased in the fed state (Figure 2).

Table 4. Summary of Pharmacokinetic Parameters After Administration of Esomeprazole DR ODT 20 mg Under Fasted and Fed Conditions

	Treatment A (Fed)				Treatment B (Fasting)			
Parameter (Unit)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
AUC_{0-t} (h*ng/mL)	18	459.79	713.46	155.17	18	844.45	797.74	94.47
AUC_{0-inf} (h*ng/mL)	15	552.64	772.01	139.70	18	858.46	809.46	94.29
Residual Area (%)	15	6.88	8.13	118.18	18	1.98	1.83	92.75
C_{max} (ng/mL)	18	164.11	208.68	127.16	18	461.52	266.66	57.78
$T_{½}$ (h)	15	1.16	0.82	70.78	18	0.84	0.36	42.44
K_{el} (/h)	15	0.81	0.40	49.64	18	0.94	0.31	33.44
Parameter (Unit)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
T_{max} (h)	18	4.49	1.49	7.00	18	1.90	0.99	4.49

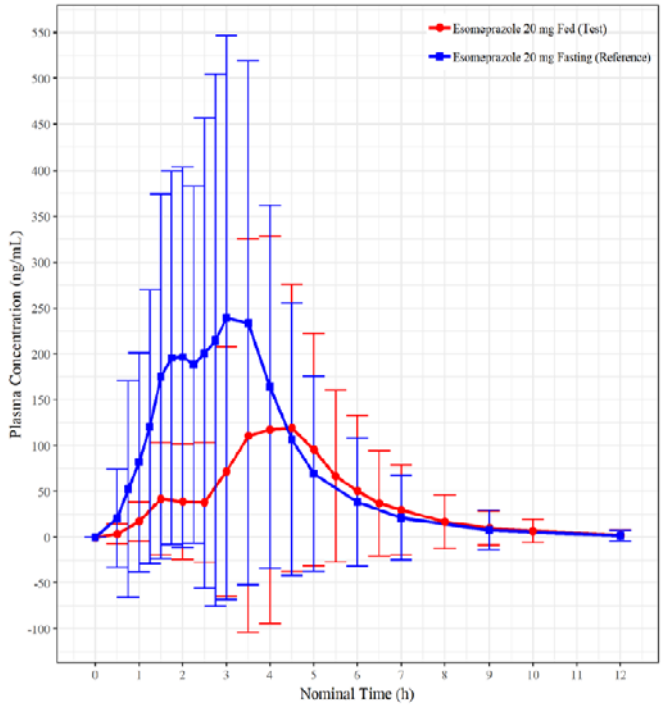
Data Source: Table 11.4.1-1 from clinical study report for Study 190031
Abbreviations: AUC = area under the concentration curve; C_{max} = maximum concentration; CV = coefficient of variation; N = number of observations; SD = standard deviation; $T_{1/2}$ = half-life; T_{max} = time to maximum concentration

Table 5. Comparison of Pharmacokinetic Parameters of Esomeprazole DR ODT Following Dosing Under Fed Versus Fasted Conditions

Parameter (Unit)	Treatment Comparisons	90% Geometric CI			Intrasubject CV (%)	Intersubject CV (%)
		Ratio (%)	Lower (%)	Upper (%)		
AUC_{0-t} (h*ng/mL)	Treatment A - Treatment B	35.86	25.04	51.34	68.05	96.23
AUC_{0-inf} (h*ng/mL	Treatment A - Treatment B	47.58	35.37	64.01	48.26	112.54
C_{max} (ng/mL)	Treatment A - Treatment B	24.29	16.01	36.86	81.90	61.05

Treatment A – 1 x 20 mg DR ODT placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed without water in fed state
Treatment B – 1 x 20 mg DR ODT placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed without water in fasted state
Data Source: Applicant's analysis adapted from Table 11.4.1-2 from clinical study report for Study 190031
Abbreviations: AUC = area under the concentration curve; C_{max} = maximum concentration; CV = coefficient of variation; DR = delayed-release; ODT = orally disintegrating tablet

Figure 2. Mean (±SD) Concentration-Time Profile for Esomeprazole Following Administration of Esomeprazole DR ODT 20 mg Under Fasted and Fed Conditions



Treatment A: Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet under fed conditions.
Treatment B: Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet under fasting conditions.

Data Source: Figure 11.4.1-1 from Table 11.4.1-1 from clinical study report for Study 190031

6.2.3. Clinical Pharmacokinetics

The single-dose pharmacokinetics of esomeprazole DR ODT were obtained from a single-center, randomized, open-label, 4-way crossover study under fasting condition. Table 6. summarizes the pharmacokinetic parameters following dosing of esomeprazole DR ODT and Nexium 24HR capsule.

Overall, the results indicated that the pharmacokinetic parameters and plasma concentration-time profiles of esomeprazole DR ODT with all three administration methods were comparable to the reference product (Nexium 24HR capsule). However, in comparing the PK parameters between the three methods of dosing of esomeprazole ODT (Table 6), it appears that the C_{max} of treatment A (place on tongue, swallow without water) was lower than the C_{max} of Treatment B (place on tongue, swallow with water) with a lower limit of the 90% geometric CI of 76.63%, which is marginally lower than the lower range of acceptance of 80%. The extent of absorption (AUC_{0-t} and AUC_{0-inf}) of Treatment A (place on tongue, swallow without water) met the bioequivalence criterion (90% CI range from 85 to 95%) to Treatment B (dosing by placing on the tongue swallowing with water) (Table 7). It must be noted that C_{max} and AUC for treatment arm A of esomeprazole ODT still met the criteria for bioequivalence to the reference product, Nexium 24HR.

Table 6. Descriptive Summary of the Pharmacokinetic Parameters for Esomeprazole DR ODT and Nexium 24HR Capsule Under Fasting Condition (Study 190030)

	Test A				Test B			
Parameter (Unit)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
AUC_{0-t} (h*ng/mL)	43	1020.73	796.23	78.01	43	1039.75	723.21	69.56
AUC_{0-inf} (h*ng/mL)	43	1036.79	811.78	78.30	43	1053.36	732.38	69.53
Residual Area (%)	43	1.75	1.78	101.82	43	1.51	0.98	64.63
C_{max} (ng/mL)	43	510.07	274.74	53.86	43	558.73	240.74	43.09
$T_{1/2}$ (h)	43	0.86	0.42	48.16	43	0.83	0.36	43.88
K_{el} (/h)	43	0.95	0.34	36.07	43	0.97	0.34	35.27
Parameter (Unit)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
T_{max} (h)	43	2.24	0.99	4.99	43	2.24	1.28	3.99

	Test C				Reference D			
Parameter (Unit)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
AUC_{0-t} (h*ng/mL)	45	1072.88	745.21	69.46	44	1096.18	787.09	71.80
AUC_{0-inf} (h*ng/mL)	45	1088.49	756.97	69.54	44	1115.74	806.25	72.26
Residual Area (%)	45	1.55	1.03	66.45	44	1.78	1.44	80.97
C_{max}(ng/mL)	45	556.10	252.66	45.43	44	565.26	292.13	51.68
$T_{1/2}$ (h)	45	0.88	0.41	45.97	44	0.95	0.43	45.72
K_{el} (/h)	45	0.93	0.35	37.66	44	0.87	0.32	37.22
Parameter (Unit)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
T_{max} (h)	45	2.24	1.24	5.01	44	1.99	0.99	4.99

Test (A): 1 x 20 mg esomeprazole delayed-release orally disintegrating tablet placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed without water.
Test (B): 1 x 20 mg esomeprazole delayed-release orally disintegrating tablet placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed with water.
Test (C): 1 x 20 mg esomeprazole delayed-release orally disintegrating tablet swallowed with water.
Reference (D): 1 x 20 mg Nexium 24HR delayed-release capsule swallowed with water.
Data Source: Table 11.4.1.1 from clinical study report for Study 190030
Abbreviations: AUC = area under the concentration curve; C_{max} = maximum concentration; CV = coefficient of variation; DR = delayed-release; K_{el} = elimination rate constant; N = number of observations; ODT = orally disintegrating tablet; SD = standard deviation; $T_{1/2}$ = half-life; T_{max} = time to maximum concentration

Table 7. Comparison of Pharmacokinetic Parameters of Esomeprazole DR ODT Following Dosing by Placing on Tongue and Swallowing With Water and Without Water

Parameter	Treatment Comparisons	90% Geometric Mean Ratio CI			Intrasubject CV (%)	Intersubject CV (%)
		Ratio (%)	Lower (%)	Upper (%)		
AUC_{0-t}	Test (A)-Test (B)	89.52	84.62	94.69	15.28	88.13
AUC_{0-inf}	Test (A)-Test (B)	89.75	84.93	94.84	14.99	87.26
C_{max}	Test (A)-Test (B)	84.03	76.63	92.13	25.27	56.54

Test (A): 1 x 20 mg esomeprazole DR ODT placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed without water.
Test (B): 1 x 20 mg esomeprazole DR ODT placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed with water.
Data Source: Applicant's analysis adapted from Table 11.4.1-2 from clinical study report for Study 190030
Abbreviations: AUC = area under the concentration curve; C_{max} = maximum concentration; CI = confidence interval; CV = coefficient of variation; DR = delayed-release; ODT = orally disintegrating tablet; SD = standard deviation

6.2.4. General Dosing and Therapeutic Individualization

Dosing Regimen
The Applicant has proposed a dosage of 20 mg (one tablet) once a day for 14 days for the treatment of frequent heartburn. The proposed dose and regimen are consistent with the approved dosing regimen for the listed drug (Nexium 24HR) and are acceptable.

Dosing Instruction in Relation to Food Intake
The Applicant has proposed labeling the product with directions "take 1 tablet before eating in the morning". This is appropriate based on the results from the food-effect study (Study 190031), which indicated that the rate and extent of absorption were decreased in the fed state. This is consistent with the language in Nexium 24HR label, which recommends "swallow 1 capsule with a glass of water before eating in the morning". The proposed dosing directions in relation to food intake are acceptable.

Dosing Instruction in Relation to Administration With or Without Water
The Applicant has proposed labeling the product with directions "place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water." The pivotal BE study conducted by the Applicant evaluated all three modes of drug administration including without water and the results indicated that dosing esomeprazole DR ODT with any of the three administration methods resulted in equivalent bioavailability to the reference product (Nexium 24HR capsule). Results from the study indicated slightly lower C_{max} when the esomeprazole ODT was allowed to disintegrate on the tongue and then swallowed without water; however, the C_{max} and AUC of esomeprazole ODT met the criteria for bioequivalence to the reference product, Nexium 24HR (Table 3).

Alcohol-Drug Interaction
The Applicant has proposed labeling the product with the directions "do not take this medicine with alcohol". The Applicant has conducted in vitro alcohol-induced dose dumping assessment

studies that indicated premature release of esomeprazole with alcohol at concentrations of ≥40%. The Applicant has requested a waiver for a clinical study to assess the effect of alcohol co-administration with their product and instead proposed the instructions in the product labeling that the product should not be taken with alcohol. Further the Applicant has hypothesized that since esomeprazole is an acid labile drug, premature release of the drug in the stomach will not lead to higher drug exposure and hence no impact on safety is expected.

The Applicant's request for an alcohol clinical study waiver appears reasonable with the proposed labeling. Refer to the Biopharmaceutics review for the assessment of the in vitro alcohol-induced dose dumping study.

6.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of this product from a clinical pharmacology perspective.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The relative bioavailability study (Study 190030) and food-effect study (Study 190031) are described in Sections 6 and 14.2 of this Review. The Applicant did not conduct any other clinical trials with the proposed esomeprazole DR ODT.

7.2. Review Strategy

No large scale, phase 3 clinical trials for safety and efficacy were conducted specifically for this product. For the efficacy of the proposed product, the Applicant is relying on the efficacy of Nexium 24HR and the reliance was justified by the relative BA study showing the equivalent bioavailability between the proposed ODT 20 mg product and Nexium 24HR 20 mg.

The clinical section of this integrated review focuses on the safety results, including the oral safety of the BA/BE Study and the food-effect Study. See Section 6 for the review of PK and relative BA results.

In addition, published literature and adverse event (AE) reports identified in postmarketing databases (FDA Adverse Event Reporting System (FAERS), World Health Organization drug alert) over a time period of collection beginning in 2014 were reviewed.

8 Clinical Assessment

8.1. Review of Safety

8.1.1. Studies Used to Evaluate Safety

Study 190030

Designed as a single-center, randomized, single-dose, 4-period, 4-sequence, crossover bioequivalence study; 45 healthy male and female subjects (>18 years of age) were enrolled to compare the ODT formulation (20 mg) to the listed drug, Nexium 24HR delayed-release tablet (20 mg) under fasted condition. The crossover variable was defined by dose administration: (A) disintegration of tablet without water, (B) disintegration of tablet with water, (C) swallowed whole with water, or (D) listed drug product swallowed with water (reference). Standard PK variables were evaluated.

The Applicant conducted safety assessments, including adverse events (AE), vital signs, electrocardiograms (ECGs), oropharyngeal assessments, and standard lab evaluations. Bioequivalence standards were consistent with FDA guidance. The total number of treatment-emergent adverse events (TEAEs) reported following administration of each treatment was low. Most TEAEs were reported as mild in severity, and the subject recovered and the event resolved. There were no relevant differences between treatment groups when comparing the number of subjects for each Preferred Term (PT) AE, with the exception of "dysgeusia" (bitter taste) which was reported most frequently in subjects who received Treatment A (product disintegrated on the tongue and swallowed without water).

Study 190031

Eighteen male and female healthy subjects (>18 years of age) completed this single center, randomized, single-dose, 2-way comparative bioavailability study designed to assess the food effect on PK of esomeprazole following administration of the ODT formulation (20 mg). Investigators conducted similar assessments as in Study 190030. Under both fed and fasting conditions, other than frequent reporting of dysgeusia, the formulation was reported to be well tolerated.

Both of the Applicant's BA/BE studies were conducted outside of the United States. However, based on the totality of safety data available for esomeprazole since original prescription approval in 2001, it is unlikely that the populations studied would provide findings different from those likely to occur in the U.S. population for whom this product would be marketed.

8.1.2. Categorization of Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 was used for coding AEs. Treatment-emergent AEs (TEAEs) were summarized for all subjects who were dosed (safety

population), as the number and percentage of subjects experiencing an AE; and were presented by treatment group, System Organ Class (SOC), and Preferred Term (PT). Each subject contributed once to each of the incidence rates, regardless of the number of occurrences. The Applicant notes that in the event of multiple occurrences for a subject, the maximal severity or relationship was used in the determination of the incidence rates.

Local tolerability (oropharyngeal) assessment data were summarized descriptively.

8.2. Focused Clinical Assessments and Findings

All subjects underwent oropharyngeal assessments (palatal, sublingual, and buccal areas) to determine local tolerability of product doses administered in the bioavailability studies. The novel component of the esomeprazole product is related to the drug delivery technology as a delayed-release ODT, while the listed drug is a delayed-release capsule. According to the Applicant, the drug substance is not expected to come in contact with the oral cavity and any oral irritations would likely be the result of exposure to excipients in the drug product.

8.2.1. Oropharyngeal Assessments

Oropharyngeal assessments were conducted at screening; prior to dosing; 15 minutes and 1 hour after dosing; and just prior to discharge from each study period, for both PK Studies 190030 and 190031. These assessments included the following parameters, evaluating eight locations in the oral cavity[6]:

1) General tolerability: erythema evaluation, oral dysfunction evaluation (representing mainly taste feeling), oral inflammation evaluation, swelling evaluation, and ulceration evaluation. For each individual assessment, if there was no abnormal sign, the result was reported as "no", while if an abnormal sign was observed, the result was reported as "yes", and the finding was described further in a different row of the spreadsheet.

2) Local tolerability: any sign of erythema, inflammation, swelling, or ulceration was assessed in the areas that were inspected (right palate area, left palate area, right sublingual area, left sublingual area, right upper buccal area, right lower buccal area, left upper buccal area, and left lower buccal area). The severity score for each individual assessment was defined as:

- Grade 0: Normal mucosa
- Grade 1: Localized mucosal erythema and/or irritation without ulceration
- Grade 2: Generalized erythema and/or irritation and induration without ulceration
- Grade 3: Ulceration, vesicles, or bullae with or without any other combination of signs

All observations were documented, including severity of any findings. The majority of subject oral evaluations were considered normal; a modest number were rated not clinically significant;

[6] NDA 214278, Clinical Summary of Safety, Module 2.7.4, page 43

and few were judged to be significant. The local tolerability (oropharyngeal) assessment revealed findings in five subjects. One subject had an ulcer at left inner cheek before dosing, considered as a non-TEAE. Four subjects had TEAEs related to the oral cavity, but none of these events were considered to be associated with the study drug.

Dysgeusia, included with the oropharyngeal findings and highlighted in Table 8 below, was considered a sensory aspect by the Applicant and not pertaining to local tolerability.

Table 8. Oropharyngeal Assessments of Studies 190030 and 190031 Pooled Data

	Study 1 - 190030			Study 2 - 190031			Total number of assessments
	Normal	Findings		Normal	Findings		
		Not clinically significant	Clinically significant findings		Not-clinically significant findings	Clinically significant findings	
General tolerability assessment							
Erythema evaluation	745	1	0	162	0	0	908
Oral dysfunction evaluation	726	12	8[1]	141	0	21[2]	908
Oral inflammation evaluation	664	80	2[3]	137	25	0	908
Swelling evaluation	746	0	0	162	0	0	908
Ulceration evaluation	742	0	4[4]	162	0	0	908
Local tolerability assessment							
Local tolerability assessment	5957	4	11[5]	1296	0	0	7,268

[1] Observation of dysgeusia/metallic taste reported in 7 subjects.
[2] Observation of dysgeusia/metallic taste reported in 10 subjects.
[3] Dry mouth sensation and pasty mouth reported in subject (b) (6)
4 Observation related to Subject (b) (6) (small ulcer in left inner chick) and subject (b) (6) (small ulcer in lip).
5 Observation related to the grade of findings in subjects (b) (6)

Source: NDA 214278, Summary of Clinical Safety, Module 2.7.4, Table 15, page 45

Details of subjects reported to have clinically significant findings are summarized in Table 9.

Table 9. Significant Oropharyngeal Findings

Subject #	Age and Gender	Race	Treatment Period of Finding	Finding	Comments
(b) (6)	27 yr old male	White	Period 2 at predose, 15 min, 1 hr	Grade 1: abrasion 2 mm right upper cheek	All remaining local tolerability assessments rated at 0
	46 yr old male	White	Period 3 at predose, 15 min, 1 hr, discharge from period	Grade 1: light gingivitis right lower buccal area	
			Period 4 at predose	Grade 3: small ulcer 0.5 cm inner, inferior lip, right side	Categorized as AE Discontinued from study by Applicant

Source: Excerpted from the Applicant's oral assessment data
Abbreviations: AE = adverse event; hr = hour; min = minute; yr = year

Clinical reviewer comment: Studies and associated oral assessments were designed for single doses of esomeprazole (between 2 and 3 total doses of the proposed esomeprazole DR ODT) and a seven-day washout period between dosing in both Studies 190030 and 190031. The study designs limited subject exposure to the proposed product and do not mirror daily 14-day dosing of esomeprazole in the nonprescription setting. This was discussed in an internal meeting and it was determined that the methodology of these studies is consistent with development of other approved nonprescription PPI ODTs (i.e., NDA 208025 lansoprazole ODT and NDA 209400 omeprazole ODT). Overall, the results of these studies, with few oropharyngeal findings, did not raise concerns for oral safety.

8.3. Major Safety Results

8.3.1. Deaths

None reported.

8.3.2. Nonfatal Serious Adverse Events

None reported.

8.3.3. Dropouts and/or Discontinuations

Two subjects discontinued from Study 190030; one withdrawal by subject and one discontinuation by Applicant due to subject lip ulceration. See Section 8.2.1, Table 9.

8.3.4. Significant Adverse Events

One significant TEAE in Study 190030 led to subject withdrawal prior to dosing in Period 4 due to a lip ulceration. The Applicant reports subject withdrawal as a precautionary measure only. The TEAE was classified as mild in severity and resolved within two days. The relationship between the TEAE and the study medication was judged as unrelated by the investigator. See Section 8.2.1, Table 9.

8.4. Other Safety Results

8.4.1. Common Adverse Events

Study 190030

A total of 46 TEAEs were reported by 22 of 45 subjects during the study: 13 TEAEs reported among 25.6% of subjects following administration of Treatment A, 16 TEAEs reported among 20.9% of subjects who received Treatment B, 11 TEAEs reported among 17.8% of subjects who received Treatment C, and six TEAEs reported among 11.4% of subjects who received Treatment D. The most commonly reported TEAEs were “dysgeusia” and “headache”, each reported by 17.8% (n=8) of subjects. Table 10 highlights the frequency of reported treatment-emergent AEs in Study 190030.

Study 190031

A total of 20 TEAEs were reported among 12 of the 18 subjects who received at least one dose of the study medication (safety population). The most commonly reported TEAE was dysgeusia, reported by 11 subjects. The number of TEAEs reported and number of subjects reporting TEAEs were similar in both fasting and fed conditions. All of the TEAEs were classified as mild in severity and had resolved as of the day of report. Table 11 summarizes the frequency of treatment-emergent AEs in Study 190031.

Table 10. Frequency of Reported Treatment-Emergent Adverse Events by Treatment Group in Study 190030

System Organ Class MedDRA® Preferred Term	Treatment Group			
Number of subjects dosed	A N=43	B N=43	C N=45	D N=44
Gastrointestinal disorders	**1 (2.3%)**	**5 (11.6%)**	**2 (4.4%)**	**3 (6.8%)**
Abdominal pain	0	1 (2.3%)	0	0
Diarrhea	0	1 (2.3%)	0	0
Dry mouth	0	2 (4.7%)	1 (2.2%)	0
Dysphagia	0	0	0	1 (2.3%)
Gingival disorder	0	0	0	1 (2.3%)
Hypoaesthesia oral	0	1 (2.3%)	0	0
Lip ulceration	1 (2.3%)	0	0	0
Nausea	0	3 (7.0%)	1 (2.2%)	1 (2.3%)
General disorders and administration site conditions	**0**	**0**	**1 (2.2%)**	**0**
Chest discomfort	0	0	1 (2.2%)	0
Infections and infestations	**1 (2.3%)**	**0**	**1 (2.2%)**	**0**
Urethritis chlamydial	1 (2.3%)	0	0	0
Vaginal infection	0	0	1 (2.2%)	0
Injury, poisoning and procedural complications	**1 (2.3%)**	**0**	**1 (2.2%)**	**0**
Post procedural discomfort	0	0	1 (2.2%)	0
Skin abrasion	1 (2.3%)	0	0	0
Musculoskeletal and connective tissue disorders	**0**	**1 (2.3%)**	**1 (2.2%)**	**0**
Back pain	0	1 (2.3%)	0	0
Neck pain	0	0	1 (2.2%)	0
Nervous system disorders	**8 (18.6%)**	**5 (11.6%)**	**4 (8.9%)**	**3 (6.8%)**
Dysgeusia	7 (16.3%)	2 (4.7%)	0	0
Headache	1 (2.3%)	2 (4.7%)	3 (6.7%)	3 (6.8%)
Somnolence	0	1 (2.3%)	1 (2.2%)	0
Psychiatric disorders	**1 (2.3%)**	**0**	**0**	**0**
Stress	1 (2.3%)	0	0	0
Reproductive system and breast disorders	**0**	**1 (2.3%)**	**0**	**0**
Dysmenorrhea	0	1 (2.3%)	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (2.2%)**	**0**
Dyspnoea	0	0	1 (2.2%)	0
Skin and subcutaneous tissue disorders	**0**	**1 (2.3%)**	**0**	**0**
Rash papular	0	1 (2.3%)	0	0
Vascular disorders	**1 (2.3%)**	**0**	**0**	**0**
Hot flush	1 (2.3%)	0	0	0
Total	**11 (25.6%)**	**9 (20.9%)**	**8 (17.8%)**	**5 (11.4%)**

MedDRA®: Medical Dictionary for Regulatory Activities, Version 22.0.
Test (A): Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed without water.
Test (B): Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet placed on the tongue and allowed to disintegrate until the particles can be swallowed and then swallowed with water.
Test (C): Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet swallowed with water.
Reference (D): Pfizer, USA (Nexium® 24HR), Esomeprazole 1 x 20 mg delayed-release capsule swallowed with water.

Source: NDA 214278, Clinical Summary of Safety, Module 2.7.4, Table 10, pages 37-38.

Table 11. Frequency of Treatment-Emergent Adverse Events in Study 190031

System Organ Class MedDRA® Preferred Term	Treatment Group	
Number of subjects dosed	A N=18	B N=18
Nervous system disorders	**9 (50.0%)**	**9 (50.0%)**
Dizziness	1 (5.6%)	0
Dysgeusia	8 (44.4%)	8 (44.4%)
Headache	1 (5.6%)	0
Somnolence	1 (5.6%)	1 (5.6%)
Total	**9 (50.0%)**	**9 (50.0%)**

MedDRA®: Medical Dictionary for Regulatory Activities, Version 22.0.
Treatment A: Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet under fed conditions.
Treatment B: Dexcel Pharma Technologies Ltd., Israel, Esomeprazole 1 x 20 mg delayed-release orally disintegrating tablet under fasting conditions.
Source: NDA 214278, Clinical Summary of Safety, Module 2.7.4, Table 11, pages 39

Clinical reviewer comment: No new safety signals are identified from AE reporting in the Applicant-conducted BA/BE studies. Dysgeusia was also noted in studies of approved PPI ODT formulations (i.e., NDA 208025 lansoprazole ODT and NDA 209400 omeprazole ODT).

8.4.2. Laboratory Findings

Clinical lab tests were performed, including chemistry, hematology, and urinalysis with urine and serum pregnancy testing at each change-over period and at study exit. Investigators used a guide of Biomedical Laboratory Reference and Acceptable Ranges. All results were reviewed and considered not clinically significant based on investigator assessments. All pregnancy tests were negative.

Clinical reviewer comment: Serum creatinine levels in 10 of the 18 subjects of Study 190031 were elevated in exit laboratory results (i.e., change ≥25% over baseline or outside of laboratory range for creatinine level). Table 12 below summarizes serum creatinine values for Study 190031(fed and fasting) subjects. Subjects in Study 190030 (fasting) did not demonstrate similar serum creatinine findings. In the information request (IR) response dated September 29, 2020, the Applicant (along with the contract research organization) explains that subject consumption of a beef stew meal in Study 190031 and post-study blood collection at approximately 2 hours after dinner likely resulted in the creatinine changes from baseline and that these changes were not clinically significant. It is generally known that creatinine elevations can occur with a meat-based meal. However, the small number of study subjects, lack of a placebo group, limited dosing (two doses total), and timing of meals contribute to the challenge in interpreting the significance of these results.

Prescription labeling for Nexium includes a warning for acute interstitial nephritis (AIN) observed in patients taking PPIs (label update December 2014).[7] *Evidence of kidney injury associated with PPIs tracked as a safety issue (NISS 392, SSID 1001781, TSI 1781) resulted in a May 14, 2020 recommendation for a prescription PPI class labeling revision from AIN to tubulointerstitial nephritis having both acute and chronic phases. Given the results of this small study (Study 190031), current Rx labeling, and recent increased FAERS reporting of adverse renal events associated with PPI use, this reviewer recommends consideration of extending the Rx PPI class warning for kidney injury (tubulointersitial nephritis) to nonprescription PPI labeling. The TSI review team notes that published data evaluating the association between PPIs and kidney injury have design limitations that limit interpretability, and have limited applicability to nonprescription PPIs, due to the prolonged exposures assessed (i.e., 2.7-13.9 years) in the studies, which is much longer than the duration of use for nonprescription PPIs that are labeled, "Do not take for more than 14 days or more often than every 4 months unless directed by a doctor".*[8]

8.4.1. Vital Signs

Vital signs were part of a screening physical examination conducted for all enrollees. The Investigators established allowable ranges based on internal Standard Operating Procedures. The ranges and measurements were acceptable.

8.4.2. Electrocardiograms

These were performed at screening and study exit. There were no clinically significant changes noted by the Applicant.

[7] https://www.accessdata fda.gov/drugsatfda_docs/label/2018/021153s053,022101s017,021957s020lbl.pdf
[8] NISS Integrated Review Memorandum, April 30, 2020

Table 12. Study 190031 Serum Creatinine Levels from Subject Case Report Files

Study 190031								
CRF Subject #	Age (in Years), and Gender	Race and/or Ethnicity	Treatment Arm A (fed)[1] or B (fasted)[2]		Lab—Serum Creatinine (Reference range 35-106 umol/L)			
			Period 1	Period 2	Screening	Exit	Change	% Change From Screening
(b) (6)[3]	35 M	Black	B	A	98	135	37	37.7
	48 F	HL	B	A	60	74	14	23.3
	32 F	HL	A	B	55	72	17	30.1
	38 M	W	A	B	74	110	36	48.6
	28 M	Black	A	B	86	114	28	32.6
	30 M	HL	B	A	80	107	27	33.8
	51 M	W	A	B	82	99	17	20.7
	30 M	W	B	A	86	110	24	27.9
	33 M	HL	B	A	83	104	21	25.3
	25 M	W	A	B	70	108	38	54.3
	43 M	W	A	B	79	95	16	20.2
[4]	26 M	W	B	A	92	125	33	35.9
	25 M	W	A	B	67	87	20	29.9
	19 M	W	B	A	74	87	13	17.6
	27 F	W	A	B	76	82	6	7.9
	28 F	W	B	A	59	67	8	13.6
	35 F	W	A	B	58	70	12	20.7
	33 M	Black	B	A	83	93	10	12.0

Source: Compiled from data files by reviewer; NDA 214278, Module 5.3.1.2, Section 16.3 CRFs for Study 190031
Abbreviations: CRF = Case Report Form; F = female; HL = Hispanic/Latino; M = male; W = white
[1]Treatment A (Test): Esomeprazole delayed-release orally disintegrating tablet 20 mg (corresponding to 22.3 mg esomeprazole magnesium trihydrate) placed on the tongue, and allowed to disintegrate until the particles can be swallowed, and then swallowed without water, under fed conditions
[2]Treatment B (Reference): Esomeprazole delayed-release orally disintegrating tablet 20 mg (corresponding to 22.3 mg esomeprazole magnesium trihydrate) placed on the tongue, and allowed to disintegrate until the particles can be swallowed, and then swallowed without water, under fasting conditions
Dose: 1 x 20 mg delayed-release orally disintegrating tablet per period
[3] Creatinine 96 umol/L at unscheduled visit 2 weeks post-exit
[4] Creatinine 87 umol/L at unscheduled visit 4 days post-exit

8.5. Safety Explorations

8.5.1. Drug-Drug Interactions

Relevant interactions have been identified in labeling and related safety risks are frequently reevaluated. Consumers are directed on the DFL to ask a doctor or pharmacist before use of esomeprazole if they are taking a prescription drug.[9]

8.5.2. Human Carcinogenicity

No new nonclinical data were submitted to support safety associated with risk for carcinogenicity. See existing data used to inform prescription[10] and subsequent nonprescription labeling associated with switch of PPIs to nonprescription marketing status.

8.5.3. Human Reproduction and Pregnancy Data

See section 8.1 of prescription labeling for esomeprazole products.[11] There are no adequate and well-controlled trials with esomeprazole in pregnant women. Epidemiologic data have not demonstrated an increased risk of poor pregnancy outcomes or congenital malformations with use during first trimester. Esomeprazole may be present in human milk. Nursing infants may be at risk with exposure to the drug. Nonprescription labeling instructs: ask a health professional before use if pregnant or nursing.

8.5.4. Pediatrics

The safety and effectiveness of esomeprazole magnesium 20 mg for nonprescription use for the indication of frequent heartburn have not been established for children. In the pediatric population, heartburn may be caused by diseases other than gastroesophageal reflux. The complications of gastroesophageal reflux (e.g., esophagitis), and/or other causes of chest pain (e.g., cardiac and respiratory etiologies), may be serious clinical conditions in children.[12,13,14] Underlying causes of

[9] https://www.accessdata fda.gov/drugsatfda_docs/label/2019/204655Orig1s011lbl.pdf
[10] https://www.accessdata fda.gov/drugsatfda_docs/label/2018/021153s053,022101s017,021957s020lbl.pdf
[11] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021153s053,022101s017,021957s020lbl.pdf
[12]Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, and Wenzl TG. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498-547.
[13]Sherman PM, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S, Orenstein S, Rudolph C, Vakil N, and Vandenplas Y. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol. 2009;104(5):1278- 1295.
[14]Rosen R, Vandenplas Y, Singendonk M, Cabana M, Dilorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, and Tabbers M. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the

heartburn in children should be evaluated by a healthcare professional and nonprescription use of PPIs in children is not considered appropriate. Therefore, pediatric studies for the nonprescription use have been waived (see additional waiver details in Section 10).

8.5.5. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

As noted in prescription labeling, doses of up to 2,400 mg, which is 120 times the usual recommended clinical dose, have been reported, and may result in a variety of symptoms including confusion, drowsiness, rapid heartbeat, nausea and vomiting. There is no known antidote for esomeprazole overdose. Dialysis is not expected to remove the extensively protein-bound esomeprazole. Treatment is symptomatic and supportive.[15]

Esomeprazole is not known to produce euphoric, stimulant, sedative, or other addictive effects most commonly associated with abuse or misuse. No potential for misuse for illegal purposes has been identified.[16] Risk of rebound acid hypersecretion has been reported in patients after stopping prolonged treatment with PPIs.[17]

8.6. Postmarket Experience

Databases used by the Applicant to support safety of esomeprazole in the nonprescription setting include the FDA Adverse Event Reporting System (FAERS) and the World Health Organization Vigibase (WHO).

Clinical reviewer comments: In the 120-day update, no new safety signal related to nonprescription PPIs (including esomeprazole) was identified and data were generally consistent with safety data previously submitted in the NDA, other than the increased reporting of kidney-related AEs during the 120-day update of FAERS safety data collection. See Table 14.

8.6.1. FAERS

The Applicant stratified available data for esomeprazole by age, gender, year of reporting, marketing status (nonprescription vs. Rx), NDA/Abbreviated New Drug Application (ANDA) number, formulation, event, dose, accumulative dose, seriousness, and reporting country. The FAERS search was conducted for reporting from 2014-2019. In total, the Applicant captured 123,913 AEs from 24,231 individuals. Of them, 2,532 consumers (13.5%) reporting 10,769 AEs (8.7%) specifically identified nonprescription products. Nexium products were reported most frequently by nonprescription consumers (96.8%), likely due to Nexium's name recognition. More females (65.8%) than males (29.4%) reported nonprescription AEs; this is similar to Rx reporting and may represent a reporting pattern. More events were reported by

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66(3):516-554.

[15] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021153s053,022101s017,021957s020lbl.pdf

[16] EMA/CHMP/498929/2013 (United Kingdom) Assessment Report: Nexium Control 2013. (EMEA/H/C/002618). European Medicines Agency.

[17] WHO Pharmaceuticals Newsletter, 2019. (Volume No.4) WHO Document Production Services, Geneva, Switzerland.

individuals aged 60-79 years in the nonprescription setting. Peak age-related reporting was slightly lower (50-69 years) in Rx esomeprazole users.

Where data were provided, 68.9% of subjects (N=888) reported taking 20 mg per day, the approved nonprescription dose strength of esomeprazole. With regard to dose effects on the quantity of nonprescription AE reporting, the Applicant notes that consumers who reported taking 10 mg doses listed 3.6 events on average, whereas subjects taking 40-80 mg reported 4.8 events on average. Rx users of 40-120 mg esomeprazole reported 8.9 events on average. There were 16 reports for subjects taking nonprescription esomeprazole products who were <18 years of age. The pediatric users were associated with 61 reported AEs. A total of 10,769 events were reported for nonprescription products; of these, 3968 (36.8%) were serious events. For the esomeprazole Rx products, 113,144 events were reported; of these, 98,323 (86.9%) were serious. Based on the total number of serious events (102,291), those associated with nonprescription products represent 3.9% of the events.

The most common events reported for nonprescription esomeprazole, as summarized in Table 13, include intentional product misuse (712 events), drug ineffective (534 events), and product use issue (516 events). The most common events reported for esomeprazole Rx products include chronic kidney disease (11,086 events), acute kidney injury (6883 events), and renal failure (6547 events). Common events reported overall included gastrointestinal disorders of upper abdominal pain, diarrhea, and nausea.

The Applicant notes that approximately 30% of the serious adverse events associated with nonprescription products reported during 2014Q1-2019Q2 and 24% of the events reported during 2019Q3-2019Q4 were associated with hospitalization. The second most common outcome code identified for 2014Q1-2019Q2 was “disabling” while “death” was the second outcome in the period covered for the 120-day safety update.[18] The proportion of each outcome code (death, hospitalization, disabling) was similar in nonprescription and Rx products; however, absolute numbers are higher in Rx esomeprazole users compared to nonprescription consumers. From 2014-2019, 45 deaths were reported for nonprescription esomeprazole use. A total of 45 cases (1.8%) receiving nonprescription drugs reported 204 events which ended in death during the 6-year period between 2014Q1-2019Q4. Twenty-six cases were reported during 2014Q1-2019Q2 and 19 cases during the period covered for the 120-day safety update.[19]

[18] NDA 214278, Summary of Clinical Safety, Module 2.7.4, pages 66-67, Table 28
[19] NDA 214278, Summary of Clinical Safety, Module 2.7.4, page 80

Table 13. Nonprescription Esomeprazole Users Reporting Common Adverse Events >4% of Total (N=2532), FAERS 2014-2019

Preferred Term	Number (%)
Intentional product misuse	703 (27.7)
Drug ineffective	526 (20.8)
Product use issue	505 (19.9)
Dyspepsia	290 (11.5)
Chronic kidney disease	232 (9.2)
Gastroesophageal reflux disease	208 (8.2)
Intentional product use issue	191 (7.5)
Off label use	179 (7.1)
Drug ineffective for unapproved indication	174 (6.9)
Diarrhea	172 (6.8)
Abdominal upper pain	164 (6.5)
Nausea	154 (6.1)
Condition aggravated	151 (6.0)
Malaise	149 (5.9)
Acute kidney injury	133 (5.3)
Abdominal discomfort	126 (5.0)
Renal failure	111 (4.4)
Renal injury	104 (4.1)
Feeling abnormal	103 (4.1)
Dizziness	103 (4.1)

Source: Summarized from NDA 214278, Clinical Summary of Safety (includes 120-Day safety), Module 2.7.4, Table 29, pages 70-73
Abbreviation: FAERS = FDA Adverse Event Reporting System

In general, data analyzed for the 120-day safety update correlated well with the original application. However, a change in the frequency of renal events (chronic kidney disease, acute kidney injury, renal failure, end stage renal disease (ESRD)) was identified in both nonprescription and Rx groups. In review of all causes of mortality in consumers of nonprescription esomeprazole products, there were 23 cases (0.98% of the total 2532 cases reported for 2014Q1-2019Q4) of acute kidney injury. These data pointed out that acute kidney failure is the most frequently reported event associated with death in consumers dosed with nonprescription esomeprazole products. Table 14 details the frequency topics of safety interest adverse events and highlights the overall incidence of reporting of acute renal injury in nonprescription and Rx esomeprazole products.

Table 14. Topics of Safety Interest Adverse Events From FAERS Database 2014-2019

	Period 2014 Q1- 2019 Q2				Period 2014 Q1 – 2019 Q4			
	Esomeprazole OTC Subject N=2317 Events= 9720		Esomeprazole Rx Subject N=12186 Events=89962		Esomeprazole OTC Subject N=2532 Events=10,769		Esomeprazole Rx Subject N=16283 Events=113,144	
	Patients N (%)	Events N (%)	Patients N (%)	Events, N (%)	Patients N (%)	Events N (%)	Patients N (%)	Events, N (%)
Acute kidney injury	76 (3.3)	106 (1.1)	2949 (24.2)	4071 (4.5)	133 (5.3)	201 (1.9)	4899 (30.1)	6883 (6.1)
Chronic kidney disease	136 (5.9)	179 (1.8)	5048 (41.4)	6526 (7.3)	232 (9.2)	328 (3.0)	8436 (51.8)	11086 (9.8)
Renal failure	63 (2.7)	89 (0.9)	2685 (22.0)	3779 (4.2)	111 (4.4)	168 (1.6)	4622 (28.4)	6547 (5.8)
End stage renal disease	43 (1.9)	62 (0.6)	1610 (13.2)	2326 (2.6)	80 (3.2)	129 (1.2)	2793 (17.2)	4113 (3.6)
Nephrolithiasis	5 (0.2)	7 (0.1)	60 (0.5)	86 (0.1)	5 (0.2)	7 (0.1)	66 (0.4)	94 (0.1)
Hypocalcemia	0	0	89 (0.7)	124 (0.1)	0 (0.0)	0	108 (0.7)	155 (0.1)
Acute generalized exanthematous pustulosis (AGEP)	1(0.0)	1 (0.0)	27 (0.1)	33 (0.0)	1 (0.0)	1 (0.0)	36 (0.2)	42 (0.0)
Acute pancreatitis	1(0.0)	2 (0.0)	19 (0.1)	33 (0.0)	1 (0.0)	2 (0.0)	21 (0.1)	35 (0.0)
Chronic pancreatitis	0	0	7	11 (0.0)	0	0	7 (0.0)	11 (0.0)
Hepatic encephalopathy	0	0	0	0	0	0	0	0
Spontaneous bacterial peritonitis	0	0	1 (0.0)	2 (0.0)	0	0	1 (0.0)	2 (0.0)

Source: NDA 214278, Clinical Summary of Safety, Module 2.7.4, Table 33, page 84
Abbreviation: FAERS = FDA Adverse Event Reporting System

Clinical reviewer comments: In a reviewer's FAERS search for narratives of reports from 2014-2019, 1,126 cases associated with Nexium 24HR and the intentional product misuse AEs by Preferred Term (PT) were found. Consistent with the Applicant's findings, a sample of reports describes use for non-OTC indications at higher doses (more than one 20 mg tablet) or for longer than allowed (>14 days). The serious cases, overall, appeared to be the result of off-label use of nonprescription esomeprazole products for Rx-only indications.

Route of Administration

In assessing the number of AEs for intravenous formulation (captured as immediate release formulation) compared to the number of events reported with the oral delayed-release formulations (capsules, tablets, oral suspension), the majority of the events are associated with the oral delayed-release formulation. The Applicant postulates that this is related to a greater user population of oral products compared to the intravenous formulation. Despite the lower number of events associated with intravenous administration, the majority of events (99.6%) were serious. A total of 82.2% of the events associated with delayed-release product are serious. The FAERS data found

do not appear to imply an increased risk of adverse events for individuals using delayed-release oral products but rather may reflect limited use of intravenous formulation.[20]

Renal Events

The number of acute kidney injury, chronic kidney disease, renal failure, ESRD and nephrolithiasis events in consumers medicating with nonprescription and Rx esomeprazole products is shown in Table 14. An increase (from application to 120-day update) in the number of acute kidney injury and chronic kidney disease AEs was observed in both nonprescription and Rx products, nearly doubling in number during the 120-day update compared to five previous years. The number of reported AEs across the spectrum of renal conditions was much greater for Rx product use; typically, more than 30x the number of nonprescription reports. This finding may be related to myriad factors (i.e., comorbidities, severity of disease, drug dose, and duration of PPI use) associated with subjects prescribed PPIs and potentially underreporting in the nonprescription setting.[21]

Hypocalcemia

Table 14 presents the number of hypocalcemia events with esomeprazole products. No hypocalcemia cases were reported for consumers using nonprescription products.[22]

Acute Generalized Exanthematous Pustulosis (AGEP)

The Applicant notes that AGEP was rarely reported in the FAERS database. A total of 37 cases were reported; of these, 36 were in the Rx group and one case was in the nonprescription group (see Table 14).

The nonprescription case was that of a 34-year-old male, treated with Nexium 24HR (204655, capsule) and hospitalized due to AGEP. The event was reported by France-AstraZeneca.[23]

Acute Pancreatitis and Chronic Pancreatitis

One case of acute pancreatitis was reported for a 30-year-old female taking Nexium 24HR for gastric ulcer hemorrhage. There were several cases reported in patients treated with Rx products for other indications. Acute pancreatitis associated with PPIs (omeprazole, pantoprazole, lansoprazole) has been reported in few cases in the literature. In a large cohort study, no significant increased risk of acute pancreatitis in users of acid-suppressing drugs was observed. The relative risk of pancreatitis is only slightly increased in comparison with taking ranitidine, cimetidine or omeprazole; however, the results of this study did not support an association between acute pancreatitis and the use of acid-suppressing drugs, though a small residual risk cannot be excluded.[24]

[20] NDA 214278, Summary of Clinical Safety, Module 2.7.4, page 83
[21] NDA 214278, Summary of Clinical Safety, Module 2.7.4, page 84
[22] NDA 214278, Summary of Clinical Safety, Module 2.7.4, page 85
[23] NDA 214278, Summary of Clinical Safety, Module 2.7.4, page 86
[24] NDA 214278, Summary of Clinical Safety, Module 2.7.4, page 86

Hepatic Encephalopathy
No cases of hepatic encephalopathy were found for nonprescription or Rx products.

Spontaneous Bacterial Peritonitis
Only one case was reported, and associated with Rx product.

Cardiovascular
The number of reported cardiovascular events is much higher with esomeprazole Rx products than in nonprescription esomeprazole products. A total of 261 (10.3%) subjects reported 345 (3.2%) events which could potentially be classified as cardiovascular events in the nonprescription group in comparison to 2573 (15.8%) subjects which reported 4114 events (3.6%) in the Rx group. Overall, cardiac events accounted for 7.7% of the events associated with nonprescription products.[25]

Nonprescription vs. Rx Adverse Events
A FAERS search by NDA numbers; formulation; dosage form; and prescription or nonprescription status, for all of the products that were reported for esomeprazole-related events, showed fewer events associated with esomeprazole nonprescription products compared to esomeprazole Rx products. The most frequently reported NDA number for a prescription esomeprazole is Nexium (NDA 021153), which is approved at higher doses (up to 40 mg) and is generally taken for longer durations. Table 15, an abbreviated table, shows the number of AEs associated with nonprescription esomeprazole.

Table 16 shows that most of the events were reported in the United States while only 2.9% of the events associated with nonprescription esomeprazole were reported by a non-U.S. country. The 120-Day Safety Update analysis showed the same pattern.

Clinical reviewer comments:
Safety issues have been addressed by relevant label warnings approved for marketed PPIs and a complete discussion of the data supporting the issues will not be repeated in this review. Where warnings are not indicated because the association with PPIs does not apply to labeled short-term use for nonprescription indications, none are listed on Drug Facts. If approved, the proposed product labeling will follow approved class labeling of nonprescription PPIs and the listed drug.

[25] NDA 214278, Summary of Clinical Safety, Module 2.7.4, page 87

Table 15. Number of Adverse Events by NDA Number From FAERS Database 2014Q1-2019Q4

NDA Number	Formulation	OTC/Rx	Dosage Form	2014Q1-2019Q2			2014Q1-2019Q4		
				Subjects (N)	Events (N)	Events (N) in M/F	Subjects (N)	Events (N)	Events (N) in M/F
204655	Esomeprazole magnesium 20 mg (Each delayed-release capsule corresponds to 22.3 mg esomeprazole magnesium trihydrate) Inactive ingredients: corn starch, D&C red no. 28, FD&C blue no. 1, FD&C red no. 40, ferric oxide, gelatin, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, pharmaceutical ink, polysorbate 80, sucrose, talc, titanium dioxide, triethyl citrate.	OTC	Delayed-release capsule	2216	9278	Male 2640 Female 6316	2373	10181	Male 3092/ Female 6733
207920	Esomeprazole magnesium 20 mg (Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate) Inactive ingredients: corn starch, crospovidone, D&C red no. 27 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, mica, microcrystalline cellulose, paraffin, polyethylene glycol, polysorbate 80, sodium stearyl fumarate, sucrose, talc, titanium dioxide, triethyl citrate.	OTC	Delayed-release oral tablet	45	330	Male 243 Female 79	78	433	Male 272/ Female 147

Source: Excerpted from NDA 214278, Clinical Summary of Safety, Module 2.7.4, Table 36, pages 90-92

Abbreviations: FAERS = FDA Adverse Event Reporting System; FD&C = Food, Drug, and Cosmetic Act; NDA = New Drug Application; OTC = over-the counter or nonprescription; Q = calendar quarter; Rx = prescription

Adverse Events by Country

Table 16. Number of Adverse Events by Reporting Country from FAERS Database 2014Q1-2019Q4

	Esomeprazole OTC				Esomeprazole Rx			
	2014Q1-2019Q2		2014Q1-2019Q4		2014Q1-2019Q2		2014Q1-2019Q4	
Country	N (events)	N (subjects)	N (events)	N (subjects)	N (events)	N (subjects)	N (events)	N (subjects)
US country	9448	2277	10,480	2,486	80,650	10,205	101,143	13,837
Non-US country	272	40	289	46	9,262	1,970	11,950	2,434
Not specified	0	0	0	0	50	11	51	12
Total	9720	2317	10,769	2,532	89,962	12,186	113,144	16,283

Source: NDA, Table 37, page 93

Abbreviations: FAERS = FDA Adverse Event Reporting System; OTC = over-the counter or nonprescription; Q = calendar quarter; Rx = prescription

8.6.2. World Health Organization (WHO) VigiBase

The Applicant searched the WHO VigiAccess database and safety-related WHO publications covering a period from 2014 to Mar 2020. A total of 92,375 records of adverse drug reactions (ADRs) were identified using the trade name Nexium. In combination with no results for Nexium 24HR, and specifics of the cases, the Applicant concludes that the majority of VigiAccess ADRs were associated with the Rx product. The most common System Organ Classes are renal and urinary disorders (35.6%); gastrointestinal disorders (32.1%); general disorders and administration site conditions (25.8%); and injury, poisoning, and procedural complications (24%). The most common ADRs (above 5%) included chronic kidney disease, acute kidney injury, renal failure, renal injury, end stage renal disease, product dose omission, GERD, dyspepsia, and drug ineffective. An increased risk for acute kidney injury and chronic kidney diseases was also reported in a large population-based health maintenance organization cohort which included patients treated with PPIs for at least 12 months.[26] The mechanism for this relationship is currently unknown.[27] Infrequently reported AEs in the WHO database include hypocalcemia reported by 152 subjects

[26] Hart E, Dunn TE, Feuerstein S, Jacobs DM. Proton Pump Inhibitors and Risk of Acute and Chronic Kidney Disease: A Retrospective Cohort Study. Pharmacotherapy. 2019;39(4):443-453. doi:10.1002/phar.2235
[27] NDA 214278, Clinical Summary of Safety, Module 2.7.4, page 101

(0.16%) and AGEP reported by 54 subjects (0.06%). There were 16 cases (0.02%) of hepatic encephalopathy and three cases (0.002%) of bacterial peritonitis.

No new safety issues were identified, and findings were consistent and included with those described in the FAERS subsection and summaries of topics of safety interest.

In a search of WHO publications, the Applicant notes two publications relevant to nonprescription PPIs. These are addressed in the Nexium 24HR DFL and Applicant proposed labeling:

1) CDAD (*Clostridium difficile*-Associated Diarrhea): The label of all nonprescription PPIs instructs the consumer to stop use the drug if they have diarrhea"[28]

2) Subacute cutaneous lupus erythematosus: The label of all nonprescription PPIs instructs consumers to stop use if they develop a rash or joint pain.[29]

The Applicant also identified during the 120-day safety update that WHO reported that acute kidney injury risk in patients treated with PPIs was added to patient information leaflets in India.

8.6.3. Literature

Published literature supports the safety and tolerability of esomeprazole delayed-release capsule, 20 mg, over a 14-day treatment course in two Phase 3 studies conducted for the approval of Nexium 24HR.[30] The most common AEs were gastrointestinal disorders. No serious AEs were reported, and no new safety signals were identified in these double-blind, placebo-controlled studies. Common AEs occurring in more than one subject are listed in Table 17. Synopses of selected articles of interest are provided below.

Peura 2014[31]
This publication summarized results of two phase 3 clinical trials used to support efficacy and safety of Nexium 24HR for nonprescription marketing. The placebo-controlled study designs included a total of 651 subjects enrolled to evaluate efficacy of a 14-day regimen of esomeprazole 20 mg for the treatment of frequent heartburn in subjects who are likely to self-treat with nonprescription medications. Adults with frequent heartburn ≥2 days per week were randomly assigned to 14-day double-blind treatment with esomeprazole (Nexium) 20 mg once daily or placebo in two identical multicenter studies. The primary efficacy outcome was percentage of heartburn-free 24-hour days across 14 days. Subjects recorded data in daily self-assessment

[28] WHO Pharmaceuticals Newsletter, 2014. (Volume No.3) WHO Document Production Services, Geneva, Switzerland.
[29] WHO Pharmaceuticals Newsletter, 2014. (Volume No.5) WHO Document Production Services, Geneva, Switzerland.
[30] Peura D A, Traxler B, Kocun C, and Lind T. (2014). Esomeprazole treatment of frequent heartburn: two randomized, double-blind, placebo-controlled trials. Postgraduate Medicine, 126(4), 33-41.
[31] Peura DA, Traxler B, Kocun C, Lind T. Esomeprazole treatment of frequent heartburn: two randomized, double-blind, placebo-controlled trials. Postgrad Med. 2014;126(4):33-41. doi:10.3810/pgm.2014.07.2781

diaries. The percentage of heartburn-free 24-hour days over 14 days was significantly higher (P <0.0001) in subjects receiving esomeprazole 20 mg compared with placebo in study 1 (N = 331; 46.13% vs. 33.07%, respectively) and study 2 (N = 320; 48.00% vs 32.75%, respectively). Treatment was generally well tolerated, with a safety profile consistent with the known AEs for esomeprazole. The most common AEs were gastrointestinal disorders (diarrhea, constipation, nausea). AEs also included nasopharyngitis, dry mouth, increased blood glucose, and decreased hemoglobin. No serious AEs were reported.

Table 17. Common Adverse Events During 14-Day Esomeprazole, 20 mg Treatment

Adverse Event	Study 1		Study 2	
	Esomeprazole 20 mg (n=168)	Placebo (n=163)	Esomeprazole 20 mg (n=165)	Placebo (n=161)
Any adverse event, n (%)	15 (8.9)	15 (9.2)	25 (15.2)	16 (9.9)
Nasopharyngitis, n (%)	2 (1.2)	1 (0.6)	0 (0)	1 (0.6)
Constipation, n (%)	1 (0.6)	2 (1.2)	2 (1.2)	0 (0)
Diarrhea, n (%)	1 (0.6)	3 (1.8)	1 (0.6)	0 (0)
Nausea, n (%)	1 (0.6)	2 (1.2)	1 (0.6)	2 (1.2)
Blood glucose decreased, n (%)	NR	NR	2 (1.2)	1 (0.6)
Blood glucose increased, n (%)	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)
Hemoglobin decreased/anemia, n (%)	1 (0.6)	0 (0)	2 (1.2)	0 (0)
Dry mouth, n (%)	NR	NR	1 (0.6)	2 (1.2)
Pain, n (%)	0 (0)	1 (0.6)	0 (0)	2 (1.2)

NR = not reported

Source: Clinical Summary of Safety, Module 2.7.4, Table 13, page 41. Reformatted from Peura et al, 2014

Peura 2018[32]

Investigators sought to determine sustained efficacy of short-term PPI therapy after treatment cessation (seven-day follow-up period after a two-week treatment period). Subjects had received treatment with esomeprazole 20 mg or placebo once daily for 14 days. Heartburn episodes were documented using daily diaries. The proportion of subjects with heartburn resolution while on treatment and during the seven days of follow-up was assessed. Predictors of resolution during this post-treatment period were evaluated. Greater run-in heartburn frequency was a significant negative predictor of heartburn resolution during follow-up (P <0.001). Among the on-treatment efficacy variables, the best predictor of resolution during follow-up was resolution during the last seven days of treatment (odds ratio: 3.81 [95% confidence interval: 2.40, 6.05; P <0.0001]). Less-frequent pretreatment heartburn, achieving heartburn resolution during the last seven days of treatment, and fewer days with heartburn throughout the treatment period were predictors of

[32] Peura DA, Le Moigne A, Wassel H, Pollack C. Sustained efficacy following resolution of frequent heartburn with an over-the-counter regimen of esomeprazole 20 mg or placebo for 14 days: two randomized trials. BMC Gastroenterol. 2018;18(1):69. Published 2018 May 22. doi:10.1186/s12876-018-0790-2

sustained heartburn resolution during the seven-day follow-up after discontinuing 14-day treatment with esomeprazole 20 mg.

Peura 2019[33]
Investigators conducted post hoc analyses of pooled data from two randomized, double-blind, placebo-controlled studies conducted in subjects with frequent heartburn and who were likely to self-treat with over-the-counter medications. The analysis correlated drug exposure and corresponding antisecretory effects of esomeprazole 20 mg on symptomatic improvement of GERD. The study population consisted of 651 adults experiencing heartburn 2 or more days per week randomly assigned to treatment with esomeprazole 20 mg or placebo once daily for 14 days following a 1-week placebo run-in period (esomeprazole: n=330; placebo: n=321). Heartburn episodes were documented in daily diaries. Change in baseline heartburn-free days across days 1–4 and 5–14 were analyzed. The greatest treatment benefit was observed during days 5–14. During this period, esomeprazole-treated subjects increased their heartburn-free time, when compared to the number of heartburn-free days during the run-in period, by 32.5%. Consistent with labeling for nonprescription esomeprazole, maximal clinical effect coincided with the estimated time of maximal esomeprazole exposure and pharmacodynamic effect, which occurs on day 5. Analyses of data from day 1 to day 4 also revealed significant benefit of esomeprazole 20 mg over placebo. Improvement over baseline was observed regardless of subject pretreatment heartburn frequency.

Johnson 2010[34]
Investigators sought to evaluate the efficacy of esomeprazole on GERD-related nighttime heartburn and associated sleep disturbances. Nighttime heartburn, common among patients with GERD, is associated with substantial clinical effects. In this multicenter, randomized, double-blind, placebo-controlled study, 262 subjects with moderate-to-severe nighttime heartburn and GERD-related sleep disturbances received esomeprazole 20 mg (n=137) or placebo (n=125) each morning for 4 weeks. Heartburn symptoms and GERD-related sleep disturbances were evaluated using the validated Pittsburgh Sleep Quality Index and validated Work Productivity and Activity Impairment Questionnaire. A total of 34.3% of subjects receiving esomeprazole achieved nighttime heartburn relief. Sleep quality, work productivity, and regular daily activities also improved significantly with esomeprazole. The overall incidence of adverse events was 21% (occurring in 30 of 143 subjects) in the esomeprazole group; nine of these events were considered treatment-related. The most common adverse events with esomeprazole treatment were nausea, headache, diarrhea, and vomiting. No serious adverse events were reported. The authors concluded that esomeprazole 20 mg is effective for patients with moderate-to-severe nighttime heartburn and GERD-related sleep disturbances, with esomeprazole improving heartburn symptoms, sleep quality, work productivity, and functionality.

[33] Peura D, Le Moigne A, Wassel H, Pollack C. Analysis of the symptom response to esomeprazole 20 mg over days 1-4 of a 14-day course of treatment for frequent heartburn: results of two randomised controlled trials. BMJ Open Gastroenterol. 2019;6(1):e000278. Published 2019 Jun 21. doi:10.1136/bmjgast-2019-000278
[34] Johnson D, Crawley JA, Hwang C, Brown K. Clinical trial: esomeprazole for moderate-to-severe nighttime heartburn and gastro-oesophageal reflux disease-related sleep disturbances. Aliment Pharmacol Ther. 2010;32(2):182-190. doi:10.1111/j.1365-2036.2010.04339.x

8.7. Summary

Esomeprazole magnesium was originally approved for prescription use in 2001 and first approved for nonprescription marketing status in 2014 (i.e., Nexium 24HR). The Applicant has proposed to market an esomeprazole DR ODT formulation and confirmed that it does not currently market this product in any foreign country.

The proposed esomeprazole product is similar to the listed drug, Nexium 24HR OTC (NDA 204655) in terms of dose, duration of dosing, and delayed-release formulation. The main difference between the two products is the dosage form (i.e., orally disintegrating tablet vs. capsule) and the administration method, i.e., disintegrated on tongue vs. swallowing whole capsule. The proposed esomeprazole formulation is an orally disintegrating drug delivery technology, described as drug substance located inside pellets (b) (4) Therefore, the active ingredient is not expected to come in contact with the oral cavity. Both proposed and listed drug products are designed for delayed release of the active substance in the intestine.

To support safe use of the proposed esomeprazole DR ODT product in the nonprescription setting, the Applicant provided safety data from its bioavailability trials (including safety data from two PK studies with oropharyngeal examinations, i.e., Studies 190030 and 190031), postmarketing data (FDA Adverse Event Reporting System (FAERS) and World Health Organization (WHO)), and published scientific literature. The Applicant also proposes a Drug Facts label (DFL) consistent with warnings and precautions of the listed drug (NDA 204655, Nexium 24HR) and appropriate maximal package size limitations.

In total, 66 treatment-emergent AEs (TEAE) were reported by 34 subjects who received at least one dose of the study drug in two bioavailability studies conducted with the ODT. Dysgeusia and headache were the most commonly reported TEAEs. The most common TEAE across both studies was dysgeusia. More subjects (N=8) reported dysgeusia with the ODT disintegrating and swallowed without water than in other test conditions of Study 190030. Eleven of 18 subjects reported dysgeusia in Study 190031. There were no serious TEAEs or deaths reported, and few oropharyngeal irritations reported based on oral assessments during the trial durations. The majority of gastrointestinal (nausea, dry mouth, diarrhea, abdominal pain) and nervous system (dysgeusia, headache, dizziness, somnolence) TEAEs were reported as mild and recovered or resolved.

The FAERS database search identified a total of 123,913 AEs from 24,231 individuals. A total of 2,532 consumers (13.5%) reporting 10,769 AEs (8.7%) specifically identified nonprescription esomeprazole products. Nexium products were reported most frequently by nonprescription consumers (96.8%) likely due to Nexium's name recognition. More females (65.8%) than males (29.4%) reported nonprescription AEs; this is similar to Rx reporting and may represent a reporting pattern. Consumers aged 60-79 years were associated with the highest frequency of reported events in the nonprescription setting.

The most common events reported in FAERS for nonprescription esomeprazole include intentional product misuse (712 events), drug ineffective (534 events), and product use issue

(516 events). Narratives for intentional product misuse cases typically described use of esomeprazole at higher than nonprescription dosing instructions and for non-OTC indications. In review of all causes of mortality in consumers of nonprescription esomeprazole products, there were 23 cases (0.98% of the total 2532 cases reported for 2014Q1-2019Q4) of acute kidney injury.

In a search of the WHO VigiAccess database covering a period from 2014Q1 to 2020Q1, 92,375 records of adverse drug reactions (ADRs) were identified using the trade name Nexium. The Applicant concluded that in the absence of findings specifically for Nexium 24HR, the majority of VigiAccess ADRs was associated with the Rx product. The most common ADRs (above 5%) included chronic kidney disease, acute kidney injury, renal failure, renal injury, end-stage renal disease, product dose omission, GERD, dyspepsia, and drug ineffective. No new safety issues were identified, and findings were consistent with those described in the FAERS summary.

The safety of esomeprazole was evaluated in over 15,000 patients (aged 18 to 84 years) in clinical trials worldwide including over 8,500 patients in the United States and over 6,500 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, esomeprazole was well tolerated in both short- and long-term clinical trials.[35] Published literature supporting approval of the listed drug (NDA 204655, Nexium 24HR), includes two randomized, double-blind, placebo-controlled studies conducted in 651 subjects with frequent heartburn and who are likely to self-treat with nonprescription medications. Subjects were randomized to 14-day treatment regimens with daily dosing of esomeprazole 20 mg or placebo. The most common study AEs were gastrointestinal disorders (diarrhea, constipation, nausea). AEs also included nasopharyngitis, dry mouth, increased blood glucose, and decreased hemoglobin. No serious AEs were reported.[36]

Overall, most of the adverse events associated with marketed esomeprazole nonprescription products were nonserious and fewer in number than with prescription products. The difference in number and severity of AEs is likely due to different treatment regimens and doses. Safety findings provided by the Applicant indicate a common safety profile for the proposed ODT product and listed drug, Nexium 24HR. In terms of types of AEs, the safety profile observed during the 120-day safety update correlates well with the original submission. However, an increase in the number of renal events was noted during this 4-month period in both nonprescription and Rx settings; the majority of these renal events were associated with Rx product.[37]

Approved for nonprescription marketing in 2014, the relied-upon listed drug Nexium 24HR has a safety profile supporting continued marketing of esomeprazole 20 mg for the nonprescription indication of frequent heartburn. The 2019 Nexium 24HR 2019 DFL includes current instructions to support safe use of esomeprazole.[38] The Applicant proposed

[35] https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022101s014021957s017021153s050lbl.pdf
[36] Peura DA, Traxler B, Kocun C, Lind T. Esomeprazole treatment of frequent heartburn: two randomized, double-blind, placebo-controlled trials. Postgrad Med. 2014;126(4):33-41. doi:10.3810/pgm.2014.07.2781
[37] NDA 214278, Summary of Clinical Safety, Module 2.7.4, page 93
[38] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204655Orig1s011lbl.pdf

an esomeprazole DR ODT product with the same dose, duration, indication, and labeled safety information as the nonprescription listed drug.

The Applicant proposes a maximum 42-count package size for the product, limited to 3 courses of 14 daily dose treatment courses per year. This is consistent with other nonprescription PPI products, for which package size limitations are based on concerns for potential overuse and misuse of the product (e.g., use for longer than directed or for conditions that should only be treated under the care of a healthcare provider).

The clinical review assessed safety data collected from two Applicant-conducted bioavailability trials in a small population of healthy subjects. Although the proposed ODT formulation was not formally tested to evaluate its safety under a full treatment course, i.e., daily administration for 14 days, the few signs of oropharyngeal irritation, and limited concerns about persistent related AEs as reported in the bioavailability trials, support approval of the proposed product for use in the nonprescription setting. It is anticipated that consumers who develop oral irritations in particular will quickly determine to stop using the product, seek another formulation, consult a healthcare provider, and/or report the event.

8.8. Recommendation

The availability of a safe profile nonprescription ODT PPI product will provide a convenient and accessible alternative, particularly for adult consumers with swallowing difficulties who seek short duration treatment of heartburn. From the clinical perspective, the submitted data support approval for NDA 214278 (esomeprazole delayed-release (DR) orally disintegrating tablet (ODT), 20 mg) for the claimed indication.

This recommendation is based, in part, on findings from the safety profile of the proposed drug as demonstrated in the bioequivalence and bioavailability studies and, in general, by safety data in the postmarketing experience of nonprescription esomeprazole products for the same indication, dose, and duration. Further review and consideration of extending Rx PPI class labeling for kidney injury (tubulointerstitial nephritis) to nonprescription PPI products is also recommended.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held for this application.

10 Pediatrics

Under the Pediatric Research Equity Act (PREA), (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The safety and effectiveness of esomeprazole magnesium 20 mg for nonprescription use for the indication of frequent heartburn have not been established for children. In the pediatric population, heartburn may be caused by diseases other than gastroesophageal reflux. The complications of gastroesophageal reflux (e.g., esophagitis), and/or other causes of chest pain (e.g., cardiac and respiratory etiologies), may be serious clinical conditions necessitating the input of a learned intermediary.[39,40,41]

Accordingly, the Applicant submitted a full waiver request for pediatric studies of all pediatric age groups under the Pediatric Research Equity Act (PREA) for the indication of frequent heartburn. The agreed initial pediatric study plan submitted under PIND 129881 on August 27, 2019 included a full pediatric waiver because the underlying causes for heartburn in children should be evaluated by a health professional and the product would be unsafe in all children for the nonprescription use.

In the August 18, 2020 Pediatric Review Committee (PeRC) PREA subcommittee meeting, the PeRC agreed with a full waiver.

[39]Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, and Wenzl TG. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498-547.
[40]Sherman PM, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S, Orenstein S, Rudolph C, Vakil N, and Vandenplas Y. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol. 2009;104(5):1278- 1295.
[41]Rosen R, Vandenplas Y, Singendonk M, Cabana M, Dilorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, and Tabbers M. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66(3):516-554.

11 Labeling Recommendations

11.1. Nonprescription Drug Labeling (Drug Facts Label)

The proposed labeling is mostly consistent with the listed drug labeling.

The major difference from the listed drug labeling is the administration method to place the ODT on tongue before administration with or without water.

In addition, the proposed "do not take this medicine with alcohol" is acceptable based on the in vitro alcohol-induced dose dumping study. The same language appears on Dexcel's currently marketed other acid-reducing products (i.e., lansoprazole and omeprazole delayed-release orally disintegrating tablets).

During the review, the statement "Wildberry Flavor" on the Principle Display Panel of this product as opposed to the (b) (4) berry flavor mixture included in the formulation was discussed. The labeling reviewer found it acceptable based on the sensory evaluation survey suggesting consumers perceived the flavor to be wildberry.

DMEPA reviewed blister container labels and note that partial instructions on how to take the product, and how to separate and open the product, appear on the blister container labels. These same partial instructions also appear on Dexcel's currently marketed acid-reducing products (i.e., lansoprazole and omeprazole delayed-release orally disintegrating tablets). DMEPA did not find any postmarketing medication errors related to these partial instructions on the blister container labels for Dexcel's currently marketed other acid-reducing products and did not recommend any revisions.

The labeling reviewers found the draft labeling submitted on September 25, 2020 and October 1, 2020 acceptable. The labeling reviewers recommend the following minor editorial revisions be included in the Approval letter.

1. In Drug Facts labeling (DFL), make the initial "i" lower case in the word "information" in the "Other information" heading.

2. Rotate the arrow in the "Inactive ingredients" heading left 90º to point the consumer to the next DFL heading (Questions) on the side panel accurately on the following labels:
   - 2-count outer carton with berries image (physician sample)
   - 2-count outer carton without berries image (physician sample)
   - 14-count inner carton with berries image
   - 14-count inner carton without berries image
   - 14-count outer carton with berries image
   - 14-count outer carton without berries image

3. Rotate the last panel of the DFL by 180 degrees so that the text does not appear upside down when following the flow of information suggested by the arrow under the "Other information" heading on the following labels:

- 28-count inner carton with berries image
- 28-count inner carton without berries image
- 42-count outer carton with berries image
- 42-count outer carton without berries image

4. Delete the three barlines enclosing the "Tips for managing heartburn" within the Drug Facts box. As proposed, the "Tips" list appears to be part of the Drug Facts box, but "Tips" is not required Drug Facts content. The list needs to appear outside of the Drug Facts box. Make this change to the following labeling:

- 28-count inner carton with berries image
- 28-count inner carton without berries image
- 42-count outer carton with berries image
- 42-count outer carton without berries image

12 Postmarketing Requirements and Commitment

None – not applicable to nonprescription products.

13 Division Director Comments

I have reviewed the data, and concur with the approval recommendation of the Cross-Discipline Team Leader, Dr. Insook Kim.

I have also carefully reviewed Dr. Lenhart's discussion of an increased frequency of reports of renal adverse events for esomeprazole, which was seen during the 120-day safety update reporting period. This increase may be due to stimulated reporting related to heavy advertising by class action law firms. Dr. Lenhart has discussed the increased reporting frequency with Dr. Valerie Pratt, Deputy Director for Safety for DNPD 1, who will continue to assess the issue. The issue is also on a list of recurring topics followed by the PPI Safety Issues Working Group. At this time, a change to class labeling for nonprescription PPIs does not appear to be warranted, but such a change may be warranted in the future, particularly if a substantial number of serious renal adverse events begins to be observed with use of the labeled nonprescription duration of use per course (14 days), or if the proportion of events reported with the nonprescription form of esomeprazole, compared to the prescription form, increases substantially.

Karen Minerve Murry, MD, FACE
Acting Deputy Director, Office of Nonprescription Drugs
Acting Director, Division of Nonprescription Drugs 1

14 Appendices

14.1. Financial Disclosure

Covered Clinical Studies: Studies 190030 and 190031

Table 18. Summary of Financial Disclosure

Was a list of clinical investigators provided?	Yes √	No ☐ (Request list from Applicant)
Total number of investigators identified: one		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
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)): N/A 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 Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests or 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)

14.2. Office of Clinical Pharmacology Appendices

The Applicant conducted two pharmacokinetic (PK) studies in healthy subjects using the to-be-marketed esomeprazole delayed-release (DR) orally disintegrating tablet (ODT): a pivotal relative bioavailability study in fasted state (Study 190030) and one food-effect study (Study 190031). The bioavailability of esomeprazole DR ODT 20 mg (proposed product) compared to Nexium 24HR delayed-release capsule under fasted condition was assessed in the pivotal relative bioavailability study (Study 190030, n=46). Results from this relative bioavailability study were used to provide a scientific "bridge" to the FDA's finding of safety and efficacy for the listed drug, Nexium 24HR (esomeprazole capsules). Study 190031 was a relative bioavailability study that compared the extent and rate of the absorption of esomeprazole DR ODT under fed and fasted conditions.

14.2.1. Relative Bioavailability Study Under Fasting Condition (Study 190030)

Study Design

This was a single-center, randomized, single-dose, open-label, 4-period, 4-sequence, crossover bioequivalence (BE) study to compare the rate and extent of absorption of a test esomeprazole delayed-release orally disintegrating tablet 20 mg placed on tongue and administered without or with water, or swallowed with water, versus Nexium 24HR, a reference esomeprazole delayed-release capsule 20 mg swallowed with water under fasting conditions.

Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme generated by the Applicant. Subjects were confined to the clinical facility from at least 10 hours prior to drug administration until after the 12.0-hour postdose blood draw, in each period.

A single oral dose of esomeprazole as a 1 x 20 mg delayed-release orally disintegrating tablet of test or 1 x 20 mg delayed-release capsule of reference was administered, in each study period. The treatment phases were separated by a washout period of seven days.

Blood samples were collected prior to study drug administration and 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 9.00, and 12.0 hours postdose in each period.

Table 19. Study Information (Study 190030)

Study Title Randomized, Open-Label, 4-Way Crossover Bioequivalence Study of Esomeprazole Delayed-Release Orally Disintegrating Tablet 20 mg and Nexium 24HR Delayed-Release Capsule (Reference) Following a 20 mg Dose in Healthy Subjects Under Fasting Conditions	
Project No.	190030
Qualified Investigator	Denis Audet, MD
Study Centers Clinical, Statistical, and Analytical: For some subjects, activities apart from confinement(s) were performed at the following facility:	Syneos Health 2500, ue Einstein Québec (Québec), Canada, G1P 0A2 Tel.: 418-527-4000 Syneos Health 5160, boul. Décarie, Suite 800 Montréal (Québec) Canada, H3X 2H9 Tel.: 514-485-7500
Dates of the Clinical Portion	First Subject First Visit: 27-MAR-2019 First Subject First Dose: 15-APR-2019 Last Subject Last Dose: 06-MAY-2019 Last Subject Last Visit: 21-MAY-2019

Table 20. Study Sample Information (Study 190030)

Source of Study Samples	Syneos Health Clinique 2500, rue Einstein Québec (Québec) Canada G1P 0A2
Storage Temperature	-20ºC
Number of Subjects Dosed	45
Number of Subjects Withdrawn	4 (Subjects (b) (6))
Subjects to be Analyzed as Per Protocol	All subjects completing at least 2 periods, including treatments for one possible comparison and subjects withdrawn from the study due to adverse events or vomiting episodes
Number of Subjects Analyzed	45
Number of Subjects Analyzed for Safety Reasons	1 (Subject (b) (6) period 4)
First Date of Analysis to Last Date of Analysis	08-MAY-2019 to 20-MAY-2019
Duration of Sample Storage: (first collection date (PK1) to last extraction date)	35 days (15-APR-2019 to 20-MAY-2019) Within the validated stability period (50 days)

Source: Bioanalytical report for study 190030

Table 21. Study Product Information (Study 190030)

Product	**Test**	**Reference**
Treatment Identification	A, B, C	D
Product Name	Esomeprazole Delayed-Release Orally Disintegrating Tablet 20 mg	Nexium 24HR (esomeprazole magnesium) Capsule 20 mg
Company Responsible for Manufacturing	Dexcel Pharma Technologies Ltd.	Marketed by: Pfizer, USA
Batch/Lot Number	BY530718	BAVWB
Manufacturing Date	August 2018	Not available
Expiration Date	June 2019 (retest date)	February 2020
Strength	20 mg	20 mg
Dosage Form	Orally disintegrating tablet	Delayed-release capsule
Bio-batch Size	(b) (4) tablets	Not available
Production Batch Size	Not available	Not available
Potency	100.7%	99.8%
Content Uniformity (mean, % CV)	AV=5.6	AV=8.2
Dose Administered	1 x 20 mg	1 x 20 mg
Route of Administration	Oral	Oral

Source: Table 9.4.2-1 from clinical study report for Study 190030

Reviewer's comment:

- *The BE study design is adequate.*
- *The plasma elimination half-life of esomeprazole after oral administration ranged between 1.2 to 1.5 hours based on the USPI for Nexium. 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 esomeprazole.*

Study Results

Summary of Demographics and Body Measurements Data of Subjects

Forty-five subjects (26 females and 19 males) were randomized and dosed in this study; of these, 43 subjects completed the study. Two subjects discontinued from the study. Subject No. (b) (6) withdrew himself after completing Period 2 and Subject No. (b) (6) was withdrawn due to adverse event (AE) "Lip ulceration" prior to dosing in Period 4. Subject Nos. (b) (6) did not turn up for Period 3 but came back for Period 4 and completed the study. Table 22 below describes the subject demographics of the pharmacokinetic (PK) population in detail.

Bioanalytical Methods and Validation

Esomeprazole in plasma samples from the study were measured using an adequately validated assay using high performance liquid chromatography with tandem mass spectrometry detection. Details of the analytical method and summary of the validation are summarized in Table 23 and Table 24.

Reviewer's comments:

- *The prestudy 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 22. Summary of Demographics and Body Measurements Data of Subjects Included in the Pharmacokinetic Population

Category		PK Population Treatment Group			
		Test (A) N=43	Test (B) N=43	Test (C) N=45	Reference (D) N=44
Age (years)	Mean ± SD	41 ± 13	41 ± 13	41 ± 13	41 ± 13
	Range	19-72	19-72	19-72	19-72
	Median	37	37	37	37
Age Groups	<18	0	0	0	0
	18-40	23 (53.5%)	23 (53.5%)	24 (53.3%)	23 (52.3%)
	41-64	19 (44.2%)	19 (44.2%)	20 (44.4%)	20 (45.5%)
	65-75	1 (2.3%)	1 (2.3%)	1 (2.2%)	1 (2.3%)
	>75	0	0	0	0
Gender	Male	17 (39.5%)	17 (39.5%)	19 (42.2%)	19 (43.2%)
	Female	26 (60.5%)	26 (60.5%)	26 (57.8%)	25 (56.8%)
Race	Asian	0	0	0	0
	Black or African American	2 (4.7%)	2 (4.7%)	2 (4.4%)	2 (4.5%)
	White	41 (95.3%)	41 (95.3%)	43 (95.6%)	42 (95.5%)
	Other	0	0	0	0
Ethnicity	Not Hispanic or Latino	35 (81.4%)	35 (81.4%)	37 (82.2%)	36 (81.8%)
	Hispanic or Latino	8 (18.6%)	8 (18.6%)	8 (17.8%)	8 (18.2%)
BMI (kg/m^2)	Mean ± SD	25.36 ± 2.49	25.21 ± 2.43	25.33 ± 2.47	25.29 ± 2.48
	Range	20.35-29.69	20.35-29.69	20.35-29.69	20.35-29.69
	Median	25.62	25.48	25.62	25.55
Height (cm)	Mean ± SD	166.7 ± 9.4	166.4 ± 9.0	167.0 ± 9.3	167.0 ± 9.4
	Range	151.5-187.0	151.5-187.0	151.5-187.0	151.5-187.0
	Median	166.5	166.5	166.5	166.8
Weight (kg)	Mean ± SD	70.79 ± 11.29	70.01 ± 10.51	70.92 ± 11.23	70.85 ± 11.35
	Range	51.20-97.80	51.20-96.00	51.20-97.80	51.20-97.80
	Median	68.40	67.20	68.40	67.80

Source: Table 14.1-2 from clinical study report for study 190030
Abbreviations: PK = pharmacokinetic; SD = standard deviation

Table 23. Summary of Analytical Method for Measurement of Esomeprazole in Human Plasma

Method SOP No.:	ANI 9668.07
Method SOP Title:	Determination of Esomeprazole in Human EDTA Plasma over a Concentration Range of 5 to 3000 ng/mL using High Performance Liquid Chromatographic Method with Tandem Mass Spectrometry Detection and using Automated Extraction
Analyte:	Esomeprazole
Internal Standard:	Omeprazole-d3
Calibration Range:	5 to 3000 ng/mL
Biological Matrix:	Human EDTA K3 Plasma
Assay Volume Required:	0.100 mL
Sample Extraction:	Automated protein precipitation
Type of Assay:	LC/MS/MS (API 4000)
Column:	X-Terra MS C18, 50 x 4.6 mm, 3.5 µm
Column Temperature:	Room temperature
Mobile Phase A:	Milli-Q type water / acetonitrile with ammonium acetate and ammonium hydroxide
Chromatographic Mode:	Isocratic
Flow Rate:	1.000 mL/min
Chromatographic Integration / Acquisition Data System:	Analyst 1.6.3, AB Sciex
LIMS:	Watson version 7.4.1, Thermo Fisher Scientific Corporation
Quantitation Method:	Peak area ratio
Calibration Regression: **Weighting Factor:**	Linear $1/C^2$ [Peak area ratios (analyte/internal standard) versus the nominal concentration of the calibration standards]
Calibration equation: **Coefficient of determination:**	$y = mx + b$ r^2

Source: Table adapted from bioanalytical report for study 190030
Abbreviations: EDTA = ethylenediaminetetraacetic acid; LC = liquid chromatography; MS = mass spectrometry; SOP = standard operating procedure

Table 24. Method Validation Summary of Analytical Method Used for Determination of Esomeprazole in Human Plasma

Full Validation Report No.:	55126AACW
Full Validation Report Title:	Validation of a High-Performance Liquid Chromatographic Method using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Esomeprazole (5 to 3000 ng/mL) in Human EDTA Plasma
Full Validation Report Effective Date:	16-MAR-2010
Validation Calibration Range:	5.00 to 3000.00 ng/mL
Accuracy and Precision (Between):	Biases: -1.84 to 1.72% CV: 3.61 to 6.43%
Accuracy and Precision (Within):	Biases: -6.13 to 3.28% CV: 1.88 to 7.58%
Within-Run Accuracy and Precision (Anticoagulant Effect- EDTA K_2 vs EDTA K_3):	Biases: -2.42 to 2.82% CV: 1.22 to 3.33%
Dilution Integrity (20-Fold):	Bias: 4.90%
Recovery Analyte:	101 – 102%
Matrix Selectivity (Including Hyperlipemic Matrix and Hemolyzed Matrix at 5%):	No significant interference observed in 8 out of 8 tested matrices for esomeprazole and internal standard. No effect on the quantitation of the analyte.
Freeze and Thaw Stability:	4 cycles at -20°C
Short-Term Stability of Analyte in Matrix:	27 h 25 min at room temperature
Long-Term Stability of Analyte in Matrix:	50 days at -20°C
Post-Preparative Stability:	71 h 55 min at room temperature
Maximum Run Size:	288 samples

Source: Table adapted from Analytical Method Validation Report No. 55126AACW
Abbreviations: CV = coefficient of variation; EDTA = ethylenediaminetetraacetic acid; h = hours

Analysis of Study Samples

Plasma samples from the study were analyzed once using a duplicate calibration curve and using four sets of quality control (QC) samples (low, intermediate, medium and high QCs) analyzed at least in duplicate (to have at least 5% of the number of study samples).

A total of 3500 study samples were analyzed (including subject analyzed for safety reason). A total of 3 re-assayed analyses (0.09%) corresponding to 3 reanalyzed study samples were performed out of the 3500 study samples. Results were confirmed by the repeat analyses and therefore there was no impact of reanalysis on the PK parameters.

A total of 228 samples were selected for the incurred sample reproducibility test to demonstrate that results obtained from study sample analysis are reproducible. A total of 99.56% 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 from the in-study analytical runs were acceptable (% bias less than 10% and % CV less than 5%).

Pharmacokinetics and BE Analysis Results

The mean BE analysis and PK parameters under fasting conditions are summarized in Table 3 and Table 6. respectively. The plots of the mean plasma levels over the sampling period are presented in Figure 1. The BE analysis conducted by the reviewer to verify the Applicant's analysis is summarized in Table 25.

Table 25. Summary of Reviewer's Statistical Analysis of Bioequivalence Assessment (Study 190030)

Test Arm	Treatment Comparison	Parameter	GMR	90% Geometric CI of GMR	
				Lower	Upper
Test A (DR-ODT placed on the tongue, allowed to disintegrate and swallowed without water)	Treatment A – Treatment D (Reference)	AUC_{0-t} (h*ng/mL)	91.28	88.52	99.84
		AUC_{0-inf} (h*ng/mL)	94.01	88.46	99.74
		C_{max} (ng/mL)	91.27	83.54	99.73
Test B (DR ODT placed on the tongue, allowed to disintegrate and swallowed with water)	Treatment B – Treatment D (Reference)	AUC_{0-t} (h*ng/mL)	103.91	98.37	109.77
		AUC_{0-inf} (h*ng/mL)	103.89	98.29	109.81
		C_{max} (ng/mL)	106.44	96.91	116.90
Test C (DR-ODT swallowed with water)	Treatment C – Treatment D (Reference)	AUC_{0-t} (h*ng/mL)	102.29	96.93	107.94
		AUC_{0-inf} (h*ng/mL)	102.11	96.74	107.78
		C_{max} (ng/mL)	103.83	94.65	113.91

Abbreviations: AUC = area under the concentration curve; CI = confidence interval; C_{max} = maximum concentration; DR = delayed-release; GMR = geometric mean ratio; ODT = orally disintegrating tablet

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 esomeprazole ODT swallowed after disintegrating on the tongue with or without water or swallowed as a whole tablet with water is bioequivalent to Nexium 24HR capsule. Bioequivalence was established for C_{max}, AUC_{0-last}, and AUC_{0-inf} (90% confidence intervals (CIs) for the geometric mean ratios were within the 0.80 to 1.25 range).*

14.2.2. Food-Effect Study (Study 190031)

Study Design

This was a single-center, randomized, single-dose, open-label, 2-way crossover BA study to assess the effect of food on the rate and extent of absorption of esomeprazole delayed-release orally disintegrating tablet 20 mg under fasting and fed conditions. Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme generated by Syneos. Subjects were confined to the clinical facility from at least 11 hours prior to drug administration until after the 12.0-hour post-dose blood draw, in each period. The treatment phases were separated by a washout period of seven days.

After a supervised overnight fast of at least 10 hours, subjects were either served a critical high fat, high caloric breakfast 30 minutes before drug administration (Treatment A) or were dosed with the drug without any food (Treatment B). The orally disintegrating tablet was placed on the subject's tongue immediately after removal from the blister unit. Subjects were instructed not to swallow saliva until the particles could be swallowed.

In case of Treatment A, subjects were served an FDA critical meal (high-fat, high-caloric breakfast) of between 800 to 1000 calories (approximately 50% of total caloric content of the meal derived from fat). The breakfast consisted of two eggs fried in butter, two slices of toast with butter, two strips of bacon, approximately 120 g of hash brown potatoes, and 200 mL of whole milk. Subjects were served a controlled meal not less than four hours postdose and at appropriate times thereafter, in each period. In case of Treatment B, subjects were served a controlled meal not less than four hours postdose and at appropriate times thereafter, in each period.

For Treatment A, a total of 19 blood samples (1 x 3 mL) were collected at predose and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.0, and 12.0 hours postdose in each period. For Treatment B, a total of 20 blood samples (1 x 3 mL) were collected at predose and 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.0, and 12.0 hours postdose in each period.

Table 26. Study Information (Study 190031)

Study Title Randomized, Open-Label, 2-Way Crossover Comparative Bioavailability Study to Evaluate the Food Effect of Esomeprazole Delayed-Release Orally Disintegrating Tablet 20 mg in Healthy Subjects	
Project No.	190031
Qualified Investigator	Denis Audet, MD
Study Centre Clinical, Statistical, and Analytical: For some subjects, activities apart from confinement(s) were performed at the following facility:	Syneos Health 2500, rue Einstein, Québec (Québec), Canada, G1P 0A2, Tel.: 418-527-4000 Syneos Health 5160, boul. Décarie, Suite 800, Montréal (Québec), Canada, H3X 2H9 Tel.: 514-485-7500
Dates of the Clinical Portion	First Subject First Visit: 12-APR-2019 First Subject First Dose: 23-APR-2019 Last Subject Last Dose: 30-APR-2019 Last Subject Last Visit: 14-MAY-2019

Table 27. Study Sample Information (Study 190031)

Source of Study Samples:	Syneos Health Clinique 2500, rue Einstein Québec (Québec) Canada G1P 0A2
Storage Temperature:	-20ºC
Number of Subjects Dosed:	18
Number of Subjects Withdrawn:	None
Subjects to be Analyzed as per Protocol:	All subjects completing the study and subjects withdrawn from the study due to adverse events or vomiting episodes
Number of Subjects Analyzed:	18
Number of Subjects Analyzed for Safety Reasons:	None
First Date of Analysis to Last Date of Analysis:	02-MAY-2019 to 09-MAY-2019
Duration of Sample Storage: (first collection date (PK1) to last extraction date)	16 days (23-APR-2019 to 09-MAY-2019) Within the validated stability period (50 days)

Data Source: Bioanalytical report for study 190031

Table 28. Study Product Information (Study 190031)

Product	Test
Treatment Identification	Treatment A (Fed), Treatment B (Fasting)
Product Name	Esomeprazole delayed-release orally disintegrating tablet
Company Responsible for Manufacturing	Dexcel Pharma Technologies Ltd., Israel
Batch/Lot Number	BY530718
Manufacturing Date	August 2018
Expiration Date	June 2019 (retest date)
Strength	20 mg
Dosage Form	Orally disintegrating tablet
Bio-batch Size	(b) (6) tablets
Production Batch Size	Not available
Potency	100.7%
Content Uniformity (mean, % CV)	AV = 5.6
Dose Administered	1 x 20 mg
Route of Administration	Oral

Data source: Table 9.4.2-1 from clinical study report for Study 190031
Abbreviations: AV = acceptance value; CV = coefficient of variation

Reviewer's comments:

- *The study design is adequate for assessment of food effect on performance of the proposed esomeprazole ODT.*
- *The plasma elimination half-life of esomeprazole after oral administration ranged between 1.2 to 1.5 hours based on the US Full Prescribing Information (FPI) for Nexium. 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 esomeprazole.*

Study Results

Summary of Demographics and Body Measurements Data of Subjects

In this study, 32 subjects were screened; of these, 21 subjects were enrolled (subjects who participated in Period 1 check-in procedures). Eighteen subjects (five females and 13 males) were randomized and dosed in this study; all the subjects completed the study.

Table 29 below describes the subject demographics of the PK population in detail.

Bioanalytical Methods and Validation

Esomeprazole in plasma samples from the study was measured using the same validated assay that was used in the pivotal BE study. Details of the analytical method and summary of the validation are summarized in Table 23 and Table 24.

Analysis of Study Samples

Plasma samples from the study were analyzed once using a duplicate calibration curve and using four sets of quality control samples (low, intermediate, medium and high QCs) analyzed at least in duplicate (to have at least 5% of the number of study samples). A total of 702 study samples were analyzed and there were no reassays.

A total of 72 samples was selected for the incurred sample reproducibility test to demonstrate that results obtained from study sample analysis are reproducible. All of the reanalyzed samples met the criteria of assay reproducibility.

The within-run and between-run accuracy and precision of calibration and quality control samples during the in-study analytical runs were acceptable (% bias less than 10% and % CV less than 5%).

Table 29. Summary of Demographics and Body Measurements Data of Subjects Included in the Pharmacokinetic Population

Category		PK Population Treatment Group	
		Treatment A N=18	Treatment B N=18
Age (years)	Mean ± SD	33 ± 8	33 ± 8
	Range	19-51	19-51
	Median	31	31
Age Groups	<18	0	0
	18-40	15 (83.3%)	15 (83.3%)
	41-64	3 (16.7%)	3 (16.7%)
	65-75	0	0
	>75	0	0
Gender	Male	13 (72.2%)	13 (72.2%)
	Female	5 (27.8%)	5 (27.8%)
Race	Asian	0	0
	Black/African American	3 (16.7%)	3 (16.7%)
	White	15 (83.3%)	15 (83.3%)
	Other	0	0
Ethnicity	Not Hispanic or Latino	13 (72.2%)	13 (72.2%)
	Hispanic or Latino	5 (27.8%)	5 (27.8%)
BMI (kg/m^2)	Mean ± SD	24.71 ± 2.63	24.71 ± 2.63
	Range	19.73-28.92	19.73-28.92
	Median	24.52	24.52
Height (cm)	Mean ± SD	171.2 ± 9.6	171.2 ± 9.6
	Range	153.0-183.5	153.0-183.5
	Median	174.0	174.0
Weight (kg)	Mean ± SD	72.82 ± 12.07	72.82 ± 12.07
	Range	47.40-91.90	47.40-91.90
	Median	72.70	72.70

Data Source: Table 14.1-2 from clinical study report for Study 190031
Abbreviation: SD = standard deviation

- *Reviewer's comment: The demographics profile is acceptable.*

Pharmacokinetics and BE Analysis Results

The mean BE analysis and PK parameters under fasting and fed conditions are summarized in Table 4 and Table 5, respectively. The plots of the mean plasma levels over the sampling period are presented in Figure 2. Mean (±SD) Concentration-Time Profile for Esomeprazole Following Administration of Esomeprazole DR ODT 20 mg Under Fasted and Fed Conditions. The BE analysis conducted by the reviewer to verify the Applicant's analysis is summarized in Table 30.

Table 30. Summary of Reviewer's Analysis of the Food-Effect Study Using BE Criterion (Study 190031)

Treatment Comparison	Parameter	GMR	90% Geometric CI of GMR	
			Lower	Upper
Fed versus fasted (Reference)	AUC_{0-t} (h*ng/mL)	36.90	26.28	51.82
	AUC_{0-inf} (h*ng/mL)	51.62	40.70	65.47
	C_{max} (ng/mL)	24.29	16.01	36.86

Abbreviations: AUC = area under the concentration curve; CI = confidence interval; Cmax = maximum concentration; GMR = geometric mean ratio

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 esomeprazole ODT swallowed after disintegrating on the tongue with or without water or swallowed as a whole tablet with water is bioequivalent to Nexium 24HR capsule. Bioequivalence was established for C_{max}, AUC_{0-last}, and AUC_{0-inf} (90% CIs for the geometric mean ratios were within the 0.80 to 1.25 range).*

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Cynthia Kim, PharmD
Office of Clinical Pharmacology Reviewer	Anand Balakrishnan, PhD
Office of Clinical Pharmacology Team Leader	Insook Kim, PhD
Clinical Reviewer and Clinical Team Leader	Martha Lenhart, MD, PhD
Cross-Disciplinary Team Leader	Insook Kim, PhD
Division Director **Division of Nonprescription Drugs 1**	Karen Minerve Murry, MD, FACE, Acting

Abbreviation: FACE = Fellow of the American College of Endocrinology

Additional Reviewers of Application

Office and/or Division	Discipline	Reviewers and Team Leaders	DARRTS Reference ID for Review
OND DNPD1	Nonclinical Reviewer	Taro Akiyama, PhD Jane Sohn, PhD (TL)	4655645
OPQ	CMC Application TL	Swapan De, PhD	4664136
	Biopharmaceutics	Rajesh Savkur, PhD (Primary) Min Li, PhD (Secondary)	
	Process	Shu-Wei Yang, PhD	
	Facility	Kamal Tiwari, PhD	
	Drug Substance	Joe Leginus, PhD	
	Drug Product	Chris Galliford, PhD	
OSE DMEPA		Grace Jones, PharmD Ashleigh Lowery, PharmD (TL) Chi-Ming (Alice) Tu, PharmD (Associate Director for Nomenclature and Labeling)	4614072
OND DNPD1	Labeling	Lori Parsons, PhD Kevin Lorick, PhD (TL)	4679024 4664499
	Associate Director for Labeling	Ruth (Betsy) Scroggs, PharmD	
OND Policy		Jagjit Grewal, MPH	

Abbreviations: OND = Office of Nonprescription Drugs; CMC = Chemistry, Manufacturing, and Controls; CDTL = Cross-Discipline Team Leader; DARRTS = Document Archiving, Reporting, and Regulatory Tracking System; DMEPA = Division of Medication Error Prevention and Analysis; DNPD1 = Division of Nonprescription Drugs 1; ID = identification number; OPQ = Office of Pharmaceutical Quality; OSE = Office of Surveillance and Epidemiology; TL = team leader

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Anand Balakrishnan, Ph.D.	OCP/DIIP	Section: 6, 14.2	**Select one:** _x Authored Approved
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 214278
Supporting document/s:	SD-1, SD-2, SD-4, SD-5, and SD-9
Applicant's letter date:	12/18/19, 2/5/20, 3/19/20, 3/20/20, and 4/20/20
CDER stamp date:	12/20/19, 2/5/20, 3/19/20, 3/20/20, and 4/20/20
Product:	Esomeprazole delayed-release orally disintegrating tablet, 20 mg
Indication:	Frequent heartburn (occurs 2 or more days a week) in adults (18 years of age and older).
Applicant:	Dexcel Pharma Technologies, Ltd.
Review Division:	Division of Non-Prescription Drug Products I (ONDPI)
Reviewer:	Taro E. Akiyama, Ph.D.
Supervisor/Team Leader:	Jane J. Sohn, Ph.D.
Acting Division Director:	Karen Mahoney, M.D.
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Disclaimer

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1 Executive Summary

1.1 Introduction

The sponsor, Dexcel Pharma Technologies, Ltd. (DPT), submitted a 505(b)(2) application for esomeprazole delayed-release orally disintegrating tablets (DR ODT), 20 mg. The proposed drug product is a proton pump inhibitor being developed by for the treatment of frequent heartburn (occurring 2 or more days a week) in adults (18 years of age and older). DPT is relying on FDA's previous findings of safety and efficacy for the listed drug, Nexium 24HR capsules (esomeprazole magnesium, NDA 204655, AstraZeneca LP), and does not propose any new clinical studies. FDA indicated in its 74-day filing review (dated March 3, 2020) that the Sponsor established an adequate scientific bridge to Nexium 24HR capsules via a bioequivalence study (Study #190030), which demonstrated that esomeprazole DR ODT is bioequivalent to Nexium 24HR capsules.

FDA also noted as a comment in the 74-day review letter that the safety justification of the excipients in the Sponsor's proposed flavoring mixture would be a review issue. In particular, FDA pointed out that Flavor and Extract Manufacturers Association of the United States (FEMA) GRAS designations for flavoring agents do not necessarily constitute an FDA determination of safety. Thus, FDA submitted an IR requesting the detailed quantitative composition and safety assessment of the proposed (b) (4) berry flavor mixture from the Sponsor and/or DMF holder. A response to the IR was provided by the Sponsor and DMF holder on March 20, 2020.

1.2 Brief Discussion of Nonclinical Findings

FDA determined that the Sponsor established a scientific bridge to the listed drug, Nexium 24HR capsules and may therefore rely on FDA's previous findings of safety and efficacy for Nexium 24HR capsules that contain that the same amount of active ingredient, 20 mg esomeprazole, as the Sponsor's proposed product, DPT ODT.

In this review, we provide a comprehensive evaluation of the safety justification for each of the excipients in the Sponsor's proposed formulation. Our analysis revealed that each of the components of the flavor mixture is adequately supported by CFR GRAS designations or by Joint FAO/WHO Expert Committee on Food Additives (JECFA) determinations. Further, the levels of each of the excipients in the proposed formulation (but not in the flavor mixture) are within levels found in FDA-approved oral products. The flavor mixture, although not found in FDA-approved oral products, is also reasonably safe. Thus, adequate safety justification for each of the excipients in the formulation has been provided from a nonclinical perspective.

In addition, the CMC group noted that impurity levels are within reporting threshold limits and the drug product has a stable impurity profile. Likewise, there is a lack of any major degradants reported. As such, there are no concerns with the compendial control of drug product impurities from the CMC perspective (email communication with Christopher Galliford, dated July 27, 2020).

In summary, adequate safety justification has been provided for the active ingredient, excipients and impurities in the Sponsor's proposed drug product from a nonclinical perspective.

1.3 Recommendations

1.3.1 Approvability

Approvable from a nonclinical perspective. Adequate safety justification has been provided for the active ingredient, excipients and impurities in the proposed drug product from a nonclinical perspective.

2 Drug Information

2.1 Drug

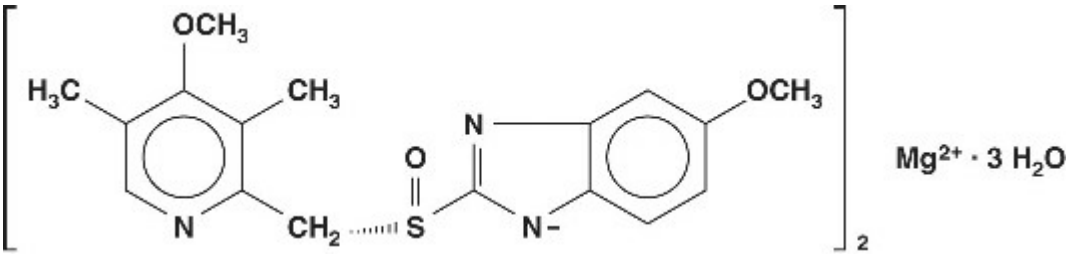
CAS Registry Number: 217087-09-7

Generic Name: Esomeprazole

Chemical Name: bis(5-methoxy-2[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate

Molecular Formula/Molecular Weight: $(C_{17}H_{18}N_3O_3S)_2Mg \times 3\ H2O$ / 767.2 grams

Structure or Biochemical Description



Pharmacologic Class: Proton Pump Inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

Dexcel Pharma Technologies proposed to rely on FDA's previous findings of safety and efficacy for the listed drug Nexium 24HR capsules (esomeprazole magnesium, NDA 204655, AstraZeneca LP).

The natural and artificial flavoring ingredients in the Sponsor's proposed (b) (4) berry flavor mixture (b) (4) are specified in DMF (b) (4) (holder (b) (4)) for which a Letter of Authorization was provided.

2.3 Drug Formulation

Listed below in Table 1 are the components of the proposed drug formulation.

Table 1: Quantitative Composition of Drug Formulation

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Listed below in Table 2 are the components of the proposed flavor mixture specified in DMF (b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients in the Sponsor's proposed formulation.

The Sponsor indicated in their meeting package (submitted December 20, 2019) that the natural and artificial flavoring ingredients in their proposed (b) (4) berry flavor mixture (b) (4) are proprietary and are specified in DMF (b) (4) (LOA provided). Since the hard copy of DMF (b) (4) was not immediately available to us, the excipients the formulation that are not in the flavor mixture were initially reviewed. The proposed

formulation (minus the flavor mixture) does not contain any novel excipients and the levels of the proposed excipients are within the amounts in other FDA-approved oral (or intraoral) products (see Table 1).

Once DMF (b) (4) was available, we determined that two of the components in the flavor mixture, (b) (4) were supported solely by FEMA numbers based on a preliminary review of the (b) (4) berry flavor mixture (b) (4). Since FEMA GRAS designations for flavoring agents do not necessarily constitute an FDA determination of safety, an IR was sent to the Sponsor requesting an adequate safety assessment of each of the ingredients in the (b) (4) berry flavor mixture from the Sponsor and/or DMF holder. A response was provided by the Sponsor on March 20, 2020. As outlined in Table 2, adequate safety justification for (b) (4) was provided based on FAO/WHO Expert Committee on Food Additives (JECFA) determinations. Likewise, the other components of the proposed flavor mixture are supported by the indicated GRAS determinations references in the CFR (Table 2).

Taken together, adequate safety justification has been provided for all of the proposed excipients in the formulation (including those in the flavor mixture). Additional nonclinical studies will not be needed to support the safety of the proposed excipients.

2.5 Comments on Impurities/Degradants of Concern

CMC noted that the impurity profile appears to be unchanged on storage under normal conditions, 25°C/60% humidity. During the review cycle, an initial concern from CMC regarding storage conditions (gastric resistance and a change in disintegration time on storage under harsher conditions) was adequately addressed by the Sponsor in their response to an IR from CMC and biopharma (SD-9 dated April 20, 2020). CMC also noted that the impurities fall below the specified reporting threshold and hold up well over 12 months at conditions 25°C/60% humidity. Likewise, there were no major degradants reported. The identified impurities are listed in Appendix, Tables 3 and 4. There are no concerns with the compendial control of DP impurities from the CMC perspective (email communication with Christopher Galliford dated 07/27/2020).

2.6 Proposed Clinical Population and Dosing Regimen

Per the filing review (dated 03/03/2020), the Sponsor established an adequate scientific bridge to the listed drug, Nexium 24HR (esomeprazole magnesium, NDA 204655, AstraZeneca LP) via a bioequivalence study (Study 190030, esomeprazole DR ODT vs. Nexium 24HR DR capsule). The Sponsor intends to rely on FDA's previous findings of safety for Nexium 24HR and does not propose any new clinical studies.

The proposed clinical population is adults 18 years of age and older and the labelled dosing regimen for esomeprazole DR ODT 20 mg is 20 mg once daily for 14 days. Due to the nonprescription setting, however, the use of this product can exceed 14 days, and therefore is considered to be for chronic intermittent use (more than 6 months over a lifetime).

2.7 Regulatory Background

The sponsor, Dexcel Pharma Technologies, Ltd. (DPT), submitted a 505(b)(2) application for esomeprazole delayed-release orally disintegrating tablets, 20 mg. The proposed drug product is a proton pump inhibitor being developed by for the treatment of frequent heartburn (occurring 2 or more days a week) in adults (18 years of age and older). DPT is relying on FDA's previous findings of safety and efficacy for the listed drug Nexium 24HR capsules (esomeprazole magnesium, NDA 204655, AstraZeneca LP). Per the filing review (dated 03/03/2020), the Sponsor has established an adequate scientific bridge to Nexium 24HR (NDA 204655) via a bioequivalence study (Study 190030, esomeprazole DR ODT vs. Nexium 24HR DR capsule), which indicated that esomeprazole DR ODT is bioequivalent to Nexium 24HR. DPT has also referenced DMF (b) (4) for their proposed (b) (4) berry flavor mixture (b) (4) and provided a Letter of Authorization from the DMF holder, (b) (4)

4 Pharmacology

4.1 Primary Pharmacology

Esomeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by inhibition of H+/K+- ATPase at the secretory surface of gastric parietal cells. The binding of esomeprazole to the (H+, K+)-ATPase enzyme is irreversible and results in inhibition of both basal and stimulated gastric acid secretion lasting longer than 24 hours. Esomeprazole is the S-isomer of omeprazole, which is a racemate of the S- and R-enantiomer. Esomeprazole has been shown to inhibit acid secretion to a similar extent as omeprazole. Rapid discontinuation of PPIs such as esomeprazole may cause a rebound effect and a short-term increase in gastric acid hypersecretion. Thus, esomeprazole doses should be gradually tapered, before discontinuing to prevent this rebound effect.

11 Integrated Summary and Safety Evaluation

The sponsor, Dexcel Pharma Technologies, Ltd. (DPT), submitted a 505(b)(2) application for esomeprazole delayed-release orally disintegrating tablets, 20 mg. The proposed drug product is a proton pump inhibitor being developed by for the treatment of frequent heartburn (occurring 2 or more days a week) in adults (18 years of age and older). DPT is relying on FDA's previous findings of safety and efficacy for the listed drug Nexium 24HR capsules (esomeprazole magnesium, NDA 204655, AstraZeneca LP). Per the 74-day filing review (dated March 3, 2020), the Sponsor established an adequate scientific bridge to Nexium 24HR (NDA 204655) via a bioequivalence study (Study 190030, esomeprazole DR ODT vs. Nexium 24HR DR capsule). The Sponsor intends to rely on FDA's previous findings of safety and efficacy for Nexium 24HR capsules that contain that the same amount of active ingredient, 20 mg esomeprazole, as the Sponsor's proposed product, DPT ODT.

In this review, we evaluated the safety of the excipients in the Sponsor's proposed formulation of their drug product. We determined that each of the components of the proposed flavor mixture is adequately supported by CFR GRAS designations and/or by JECFA determinations. In addition, the levels of each of the excipients in the proposed formulation (not in the flavor mixture) are within levels found in FDA-approved oral products. Thus, adequate safety justification for each of the excipients in the formulation has been provided.

In addition, CMC noted that impurity levels are within reporting threshold limits and the drug product has a stable impurity profile. In addition, there is a lack of any major degradants reported. As such, there are no concerns with the compendial control of drug product impurities from the CMC perspective (email communication with Christopher Galliford dated 07/27/2020).

An assessment of extractable and leachables is not required for proposed dosage form.

In summary, adequate safety justification has been provided for the active ingredient, excipients and impurities in the proposed drug product from a nonclinical perspective.

12 Appendix/Attachments

Table 3: Summary of Identified Impurities Results for Esomeprazole Delayed-Release Orally Disintegrating Tablets, 20 mg

(Table provided by CMC reviewer, Christopher Galliford)

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JANE J SOHN
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I concur.