CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214278Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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

Date of This Memorandum:	October 5, 2020
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPD I)
Application Type and Number:	NDA 214278
Product Name and Strength:	Esomeprazole Delayed-Release Orally Disintegrating Tablets, 20 mg
Applicant/Sponsor Name:	Dexel Pharma Technologies LTD
OSE RCM #:	2020-82-1
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 25, 2020 and on October 1, 2020 for Esomeprazole Delayed-Release. Division of Nonprescription Drugs I (DNPDI) requested that we review the revised container labels and carton labeling for Esomeprazole Delayed-Release (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

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

Of note, the Applicant indicated in their response to the September 18, 2020 Information Request that they did not print the expiration date format on the submitted revised carton labeling but that they intend to print the numerical characters, YYYY/MM, on the final carton labeling.[b]

[a] Jones G. Label and Labeling Review for Esomeprazole Delayed-Release Orally Disintegrating Tablets (NDA 214278). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 26. RCM No.: 2020-829.
[b] Kim C. General Advice Letter for Esomeprazole Delayed-Release Orally Disintegrating Tablets, NDA 214278. Silver Spring (MD): FDA, CDER, OND, DNPD I (US); 2020 SEP 25.

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

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/s/

GRACE JONES
10/05/2020 02:08:17 PM

ASHLEIGH V LOWERY
10/06/2020 02:56:48 PM

Addendum Labeling Review for Esomeprazole Delayed-Release Orally Disintegrating Tablets, 20 mg
Draft Labeling

SUBMISSION DATES:	December 20, 2019 September 25, 2020 October 1, 2020
NDA/SUBMISSION TYPE:	NDA 214278/Original NDA
ACTIVE INGREDIENT:	Esomeprazole magnesium trihydrate, 22.3 mg (esomeprazole, 20 mg, per the USP Salt Policy)
DOSAGE FORM:	Delayed-Release Orally Disintegrating Tablet
APPLICANT:	Dexcel Pharma Technologies, Ltd. Authorized U.S. Agent: CBR International Corp.® Monica Rohrschneider, Ph.D. Email: mrohrschneider@cbrintl.com
REVIEWER:	Lori Parsons, PhD (Interdisciplinary Scientist, IDS)/DNPD I/ONPD
TEAM LEADER:	Kevin Lorick PhD/DNPD I/ONPD
PROJECT MANAGER:	Helen Lee PharmD/DNPD I/ONPD

I. BACKGROUND

Dexcel Pharma Technologies, Ltd. (Dexcel) and its Authorized U.S. agent, CBR International Corp.®, 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.

This review is an addendum to the draft labeling review uploaded in to the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) on September 1, 2020. This addendum documents the resolution of labeling issues outlined in the September 1, 2020 draft labeling review as well as the general advice letter sent to Dexcel on September 18, 2020.

A general advice letter was sent to Dexcel on September 18, 2020 and requested the following labeling revisions:

All outer carton labeling:

1. Submit the package insert for review or delete reference to the package insert in the following statement that appears on the top panel of the proposed outer carton labeling: "KEEP THE CARTON AND PACKAGE INSERT. THEY CONTAIN IMPORTANT INFORMATION."

2. We note that "24h" appears on the proposed principal display panel (PDP) adjacent to the "Treats Frequent Heartburn!" flag. We recommend using either "24 hr" or "24 hour" to communicate the dosing interval clearly (once every 24 hours) of this drug product. Capitalization preference of "hr" or "hour" is deferred to you.

3. Increase the prominence of "TABLETS" in the proposed declaration of net quantity by using boldface type. Also, increase the font size to be the same as that of the numerical value in the declaration of net quantity. As proposed, the prominence of "TABLETS" in the declaration of net quantity is reduced in comparison to the numerical value, both in terms of boldface type and font size.

Drug Facts Labeling:

4. Replace "delayed-release tablet" with "delayed-release orally disintegrating tablet" in the equivalency statement within the Active ingredient heading to reference the dosage form accurately. Although the Active ingredient heading in the proposed Drug Facts label contains an equivalency statement "(Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate)," it is incomplete because the "delayed-release tablet" phrase includes only part of the dosage form name of this drug product, which is a recognized dosage form (i.e., delayed-release orally disintegrating tablet) on its own.
Add the statement "keep product out of high heat and moisture" under the Other information heading.

2-count outer carton labeling:

5. Add the statement "May take 1 to 4 days for full effect" to the 2-count outer cartons.

6. We recommend that you add the statement "First 2 doses of a 14-day course of treatment" to the PDP, to provide clarity to consumers on how the sample doses fit into the set treatment course for the drug product. The proposed statement "Follow samples with a 14-day course of treatment" is located below the declaration of net quantity on the 2-count sample outer cartons. The previously approved statement on the sample outer cartons for Nexium 24HR® is this more informative statement ("First 2 doses of a 14-day course of treatment") and is

located below the declaration of net quantity on the PDP.

Other:

7. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the lot number and expiration date format you intend to use throughout your blister container labels and carton labeling. The proposed container labels and carton labeling contain a placeholder for the lot number and expiration date and as currently presented, the format for the expiration date is not defined in the carton labeling. We recommend that the human-readable expiration date on the drug package label includes a year, month, and non-zero day. We recommend that the expiration date appears in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD format if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.

8. For consistency, add the header "Batch No." to the proposed blister container labels. The header "Batch No." appears on the carton labeling but not on the blister container labels.

Dexcel responded by submitting revised labels and a cover letter on September 25, 2020.

DNPD 1 requested Drug Facts Label (DFL) font and format specifications for the 42-count outer carton labels (with and without berries image) on September 28, 2020 as they were missing. DFL font and format specifications are needed to confirm compliance with 21 CFR 201.66. Dexcel responded on October 1, 2020 with submission of 42-count outer carton labels (with and without berries image) containing DFL font and format specifications.

Submitted Labeling	Representative of Following SKUs	Submission Dates
2-count immediate container (blister)	None	December 20, 2019 Revised: September 25, 2020
7-count immediate container (blister)	None	December 20, 2019 Revised: September 25, 2020
2-count outer carton with berries image (physician sample)	None	December 20, 2019 Revised: September 25, 2020
2-count outer carton without berries image (physician sample)	None	December 20, 2019 Revised: September 25, 2020
14-count inner carton with berries image	None	December 20, 2019 Revised: September 25, 2020
14-count inner carton without berries image	None	December 20, 2019 Revised: September 25, 2020
14-count outer carton with berries image	None	December 20, 2019 Revised: September 25, 2020
14-count outer carton without berries image	None	December 20, 2019 Revised: September 25, 2020
28-count outer carton with berries image	None	December 20, 2019 Revised: September 25, 2020
28-count outer carton without berries image	None	December 20, 2019 Revised: September 25, 2020
42-count outer carton with berries image	None	December 20, 2019 Revised: September 25, 2020 Resubmitted: October 1, 2020
42-count outer carton without berries image	None	December 20, 2019 Revised: September 25, 2020 Resubmitted: October 1, 2020

For comparison purposes, the proposed outer carton labeling in NDA 214278 was compared to the listed drug (esomeprazole delayed-release capsules (NDA 204655, S-011), most recently

approved on April 4, 2019. Additionally, the directions for use labeling elements were compared to two approved nonprescription proton pump inhibitors (PPIs) that are delayed-release orally disintegrating tablet (DR ODT) formulations, NDA 209400, S-007 and NDA 208025, S-008 (also marketed by Dexcel); most recently approved on April 29, 2020 and April 9, 2019, respectively. Also, the listed drug utilizes bottles as the immediate container, whereas this original NDA 214278 proposes to use blister packaging. Therefore, NDA 208025, S-006, approved on November 30, 2017 (also marketed by Dexcel) was used for comparison purposes of the immediate container labels.

II. REVIEWER'S COMMENTS

A. 14-, 28-, and 42-count outer cartons without an image of a berry cluster.

i. Outer Carton Label Outside Drug Facts Label

a. The statement "Treats **Frequent** Heartburn!" in blue font on a yellow banner appears with the descriptor "24HR" on a black background encircled by yellow and blue arrows on the upper, left section of the PDP.

Comment: This is acceptable.

b. The statement: "Melts in your mouth Dissolves without water" appears in white font on a red banner below the statement of identity.

Comment: This statement is previously approved in the labeling of other nonprescription PPIs (NDA 209400 and NDA 208025) and is intended to reiterate the dissolving nature of the DR ODT formulation. As in the case with these other NDAs, the pharmacokinetics data (Studies 190030 and 190031) submitted to support this NDA and its labeling received an approval recommendation from the clinical pharmacology reviewer team. This is acceptable.

c. The declaration of net quantity appears on the left, lower corner of the PDP and states: "**X TABLETS**."

Comment: This is acceptable.

d. The following statement appears on the top panel of the outer carton: "KEEP THE CARTON. IT CONTAINS IMPORTANT INFORMATION."

Comment: This is acceptable.

e. For the 2-, 14-count outer cartons (with and without an image of a berry cluster), and 14-count inner cartons (with and without an image of a berry cluster): the last DFL arrow located within the Inactive ingredients heading is facing the incorrect way (downward). The arrow is to be rotated left 90º as the last DFL heading (Questions) is to the right. The consumer should be pointed to the right when moving from the Inactive ingredients heading to the Questions heading.

Comment: Add a minor editor revision note to the action letter informing Dexcel to rotate the arrow located in the Inactive ingredients heading left 90º. This will point the consumer to the next the DFL heading (Questions) on the side panel accurately.

ii. Outer Carton Drug Facts Label

a. ***Active ingredient/Purpose***

The following appears in the Active Ingredient heading:

Active ingredient (in each tablet) Purpose
Esomeprazole 20 mg_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Acid reducer
(Each delayed-release orally disintegrating tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate)

Comment: This is consistent with the other approved nonprescription PPIs that apply the USP Salt Policy (e.g., NDAs 21229, 204544, and 207920). This is acceptable.

b. ***Directions***
The Directions heading contains the following statements:

Directions
■ adults 18 years of age and older
■ this product is to be used once a day (every 24 hours), every day for 14 days
■ may take 1 to 4 days for full effect

14-Day Course of Treatment
■ take 1 tablet before eating in the morning
■ do not crush or chew tablets
■ place the tablet on tongue; tablet disintegrates, with or without water.
The tablets can also be swallowed whole with water.
■ take every day for 14 days
■ do not take more than 1 tablet a day
■ do not use for more than 14 days unless directed by your doctor
■ do not take this medicine with alcohol

Repeated 14-Day Course (if needed)
■ you may repeat a 14-day course every 4 months
■ do not take for more than 14 days or more often than every 4 months unless directed by a doctor

■ children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.

Comment: The directions differ from the listed drug (esomeprazole delayed-release capsules/NDA 204655/Nexium 24HR®) as the listed is not an ODT formulation and therefore, does not include directions to place the tablet on tongue; tablet disintegrates, with or without water, or the option to swallow without water. Additionally, the bulleted statement "do not take this medicine with alcohol" (Directions heading) is not found in the listed drug's DFL. However, the directions for use do align with other nonprescription DR

ODT PPI drug products (e.g., NDAs 208025 and 209400). Clinical pharmacology and biopharmacology experts reviewed the submitted bioequivalence studies (Studies 190030 and 190031) assessing elements that impact directions to take the drug product with or without water; and the in vitro alcohol dose dumping study (Section 3.4 in Module 2.7.1). Both clinical pharmacology and biopharmacology teams recommended an approval. This labeling component is acceptable.

c. Other Sections/Issues

i. The Other Information heading appears with the following bulleted statements:

Other Information
■ read the directions and warnings before use
■ keep the carton. It contains important information.
■ store at 20-25°C (68-77°F); keep product out of high heat and moisture
■ store in the original package

Comment: This complies with 21 CFR 201.66(c)(7) and is acceptable. Chemistry Manufacturing Controls experts were contacted in agreement with the statement "keep product out of high heat and moisture" being included in the DFL.

ii. The DFL meets the format specifications outlined in 21 CFR 201.66.

Comment: This is acceptable.

iii. Immediate Container Label
2- and 7-count immediate container (blister pack) labels

a. "Batch No. 00000000" and "EXP YYYY/MM" appears on each blister unit containing a tablet running down each blister unit.

Comment: This is acceptable.

b. An empty blister unit in the lower, left corner of the blister pack contains abbreviated directions. The abbreviated directions state:

Place tablet on tongue; tablet disintegrates, with or without water. Do not crush or chew tablets. One 14-day course of treatment. Take 1 tablet every day for 14 days. Do not take for more than 14 days or more often than every 4 months

unless directed by a doctor.

Comment: The directions differ from the listed drug (esomeprazole delayed-release capsules/NDA 204655/Nexium 24HR®) as the listed is not an ODT formulation and therefore, does not include directions to place the tablet on tongue; tablet disintegrates, with or without water, or the option to swallow without water. However, the directions for use do align with other nonprescription DR ODT drug products (e.g., NDAs 208025 and 209400). Clinical pharmacology and biopharmacology experts reviewed the submitted bioequivalence studies (Studies 190030 and 190031) assessing elements that impact directions to take the drug product with or without water. Both clinical pharmacology and biopharmacology teams recommended approval. This labeling component is acceptable.

B. 2-count outer cartons without an image of a berry cluster.
See sections II.A.i-iv, except item g.

i. Outer Carton Label Outside Drug Facts Label

a. The statement "First 2 doses of a 14-day course of treatment" is added to underneath the declaration of net quantity. The statement appears in navy blue boldface type.

Comment: This is acceptable. This statement is consistent with the labeling of the sample configuration for the listed drug for this NDA (esomeprazole DR capsules/NDA 204655/Nexium 24HR®). Most importantly, the statement "First 2 doses of a 14-day course of treatment" is intended to provide clarity to consumers on how the two sample doses fit into the full 14-day treatment course.

b. The statement "May take 1 to 4 days for full effect" is present on the PDP.

Comment: This is acceptable. Statements such as "24HR" and "24 Hour" statements are acceptable on currently marketed nonprescription PPI labels when the statement "May take 1 to 4 days for full effect" is also present on the PDP (recent precedent NDA 22032, S-041, approved on April 8, 2019). The product is taken once every 24 hours and the accompanying statement "May take 1 to 4 days for full effect" is intended to inform consumers about the expectation of heartburn relief starting to take effect in 1 to 4 days. The PDP contains "24HR" and the accompanying statement "May take 1 to 4 days for full effect."

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted esomeprazole magnesium trihydrate, 22.3 mg (esomeprazole, 20 mg, per the USP Salt Policy) delayed-release orally disintegrating tablets labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to the following labeling submitted on September 25, 2020 (labels 1-10 below) and October 1, 2020 (labels 11-12 below):

1. 2-count immediate container (blister)
2. 7-count immediate container (blister)
3. 2-count outer carton with berries image (physician sample)
4. 2-count outer carton without berries image (physician sample)
5. 14-count inner carton with berries image
6. 14-count inner carton without berries image
7. 14-count outer carton with berries image
8. 14-count outer carton without berries image
9. 28-count outer carton with berries image
10. 28-count outer carton without berries image
11. 42-count outer carton with berries image
12. 42-count outer carton without berries image

Request the following minor editorial revision:

Rotate the arrow in the Inactive ingredients heading left 90º so that the consumer is pointed 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

Inform the sponsor that if they are interested in marketing other package configurations in the future (e.g. individual containers containing greater than 14-count, total package sizes greater than 42-count), we expect submission of a prior approval supplement that includes data to demonstrate consumer comprehension of use.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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/s/

LORI N PARSONS
10/01/2020 07:47:12 AM

KEVIN L LORICK
10/01/2020 08:27:15 AM
I concur with the review and recommendations.

Labeling Review for Esomeprazole Delayed-Release Orally Disintegrating Tablets, 20 mg *Draft Labeling*

SUBMISSION DATES:	December 20, 2019
NDA/SUBMISSION TYPE:	NDA 214278/Original NDA
ACTIVE INGREDIENT:	Esomeprazole magnesium trihydrate, 22.3 mg (esomeprazole, 20 mg, per the USP Salt Policy)
DOSAGE FORM:	Delayed-Release Orally Disintegrating Tablet
APPLICANT:	Dexcel Pharma Technologies, Ltd. Authorized U.S. Agent: CBR International Corp.® Monica Rohrschneider, Ph.D. Email: mrohrschneider@cbrintl.com
REVIEWER:	Lori Parsons, Ph.D (Interdisciplinary Scientist, IDS)./DNPD I/ONPD
TEAM LEADER:	Kevin Lorick Ph.D./DNPD I/ONPD
PROJECT MANAGER:	Helen Lee Pharm.D./DNPD I/ONPD

I. BACKGROUND

Dexcel Pharma Technologies, Ltd. (Dexcel) and its Authorized U.S. agent, CBR International Corp.®, 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 USP Salt Policy) delayed-release (DR) orally disintegrating tablet (ODT) as a drug product for the nonprescription treatment of frequent heartburn (occurs 2 or more days a week) in adults 18 years and older. 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). This same applicant also has an approved DR ODT formulation for other nonprescription proton pump inhibitors for the same

indication, using the same ODT platform (NDA 208025: lansoprazole DR ODT, 209400: omeprazole DR ODT).

The proposed drug product under review in NDA 214278, as with the Dexcel's other NDAs (NDAs 22032, 209400, 208025) does not have a proprietary name. Instead these products are marketed using the established name of the active ingredient. Dexcel plans to also market the proposed drug product using the established name of the active ingredient (esomeprazole, 20 mg).

The proposed listed drug for this original NDA is esomeprazole, 20 mg DR capsules (Nexium 24HR®/NDA 204655). Esomeprazole is a proton pump inhibitor (PPI) that inhibits the enzyme on the surface of gastric parietal cells responsible for acid production, the H^+/K^+ ATPase, leading to a reduction in gastric acid secretion, and subsequently an increase in the gastric pH.[1] Multiple PPIs are available in the nonprescription market currently in the US, However, if approved, this would be a new dosage form of esomeprazole available to consumers in the nonprescription setting. An advantage to orally disintegrating tablet dosage forms is that they provide consumers the option to administer the drug product with or without water, allowing the consumer to avoid swallowing a tablet if they choose to allow the tablet to disintegrate. An intention of the ODT formulation is to increase the ease of swallowing a whole tablet as the tablet is able to disintegrate in the oral cavity.

Currently, there are numerous PPIs marketed in the United States. The first approved PPI was omeprazole as a prescription drug in 1989 and then as a nonprescription drug product in 2003. The prescription PPI drug products are indicated for more serious conditions which require a healthcare provider's care, including duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, erosive esophagitis, and pathological hypersecretory conditions. The indication for the class of nonprescription PPIs are limited to the treatment of frequent heartburn. Note, per the June 20th, 2003 precedent-setting approval letter for NDA 021-229, Prilosec OTC®, all nonprescription PPIs have a package size limitation on individual containers not being greater than 14-count (single treatment course) and total package sizes no greater than 42-count (three treatment courses, or one year of treatment). Package sizes greater than the above-mentioned quantities require a prior approval supplement that includes data to demonstrate consumer comprehension of use. This precedent is still scientifically valid.

The application was filed, and an information request was sent to the applicant on April 3, 2020 requesting clarification on the flavor of the drug product. The original NDA submission included documentation of a (b) (4) berry flavor (see section 3.2.P.1, Description and Composition of the Drug Product in the eCTD dated December 20, 2019), yet the labeling contained references to wildberry flavor on the principal display panel (PDP), both in terms of text "Wildberry Flavor" and imagery (i.e., image of a cluster of berries including raspberry, blueberry, and blackberry). Dexcel responded on April 9, 2020 by clarifying that the drug product contains (b) (4) berry flavor which is also found in another marketed product by Dexcel (NDA 22032, omeprazole delayed-release tablets, no proprietary name). The NDA 22032 product, (b) (4) , is marketed as wildberry mint.

[1] Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut Liver. 2017;11(1):27-37. doi:10.5009/gnl15502

Submitted Labeling	Representative of Following SKUs	Submission Dates
2-count immediate container (blister)	None	December 20, 2019
7-count immediate container (blister)	None	December 20, 2019
2-count outer carton with berries image (physician sample)	None	December 20, 2019
2-count outer carton without berries image (physician sample)	None	December 20, 2019
14-count inner carton with berries image	None	December 20, 2019
14-count inner carton without berries image	None	December 20, 2019
14-count outer carton with berries image	None	December 20, 2019
14-count outer carton without berries image	None	December 20, 2019
28-count outer carton with berries image	None	December 20, 2019
28-count outer carton without berries image	None	December 20, 2019
42-count outer carton with berries image	None	December 20, 2019
42-count outer carton without berries image	None	December 20, 2019

For comparison purposes, the proposed outer carton labeling in NDA 214278 was compared to the listed drug (esomeprazole DR capsules (NDA 204655, S-011), most recently approved on April 4, 2019. Additionally, the directions for use labeling elements were compared to two approved nonprescription PPIs that are DR ODT formulations, NDA 209400, S-007 and NDA 208025, S-008 (also marketed by Dexcel); most recently approved on April 29, 2020 and April 9, 2019, respectively. Also, the listed drug utilizes bottles as the immediate container, whereas this original NDA proposes to use blister packaging. Therefore, NDA 208025, S-006, approved on November 30, 2017 (also marketed by Dexcel) was used for comparison purposes of the immediate container labels.

II. REVIEWER'S COMMENTS

A. 14-, 28-, and 42-count outer cartons without an image of a berry cluster.

i. Outer Carton Label Outside Drug Facts Label (DFL)

a. The NDC number appears on the upper, left corner of the PDP.

Comment: This complies with 21 CFR 201.2 and is acceptable.

b. The statement "Treats **Frequent** Heartburn!" in blue font on a yellow banner appears with the descriptor "24h" on a black background encircled by yellow and blue arrows on the upper, left portion of the PDP.

Comment: An information request with a labeling revision is recommended.

The nonprescription indication for this product, and the class of nonprescription PPIs, is to treat frequent heartburn, which is defined as heartburn occurring 2 or more days a week. Therefore, the statement "Treats Frequent Heartburn" is acceptable. Statements such as "24HR" and "24 Hour" are acceptable on currently marketed nonprescription PPI labels when the statement "May take 1 to 4 days for full effect" is also present on the PDP (recent precedent NDA 22032, S-041, approved on April 8, 2019). The product is taken once every 24 hours and the accompanying statement "May take 1 to 4 days for full effect" is intended to inform consumers about the expectation of heartburn relief starting to take effect in 1 to 4 days.

Most of the proposed labels (14-, 28-, and 42-count configurations) in NDA 214278 contain the accompanying statement "May take 1 to 4 days for full effect." The statements "May take 1 to 4 days for full effect," "Treats **Frequent** Heartburn!**" and "24HR" are approved labeling statements for the listed drug (esomeprazole DR capsules (NDA 204655/Nexium 24HR®). However, it is noted that the proposed descriptor is not "24HR" or "24 HOUR", instead "24h" is proposed. It is unclear if the proposed text is inadvertent as the text appears as an incomplete abbreviation. Therefore, it is recommended that an information request be sent to Dexcel to revise the proposed statement "24h" to include a complete abbreviation of "hr" or "hour" fully spelled out. This revision will provide consistency with "hr" and "hour" terminology in nonprescription PPI class labeling and clarity in communication to the consumer. Capitalization will be the choice of Dexcel. A final reviewer comment on acceptability of the proposed statement will be made in the labeling addendum subsequent to receiving the information request response.**

c. The statement "MELTech™ Melts In Your Mouth" with a stylistic "M" appears in blue font on the upper, right corner of the PDP.

Comment: This is acceptable. This statement was originally approved during another NDA marketed by Dexcel, NDA 208025, S-007 (approved November 7, 2017), which is also a DR ODT formulation. A label comprehension study report was submitted to support the proposed statement in NDA 208025, S-007 (lansoprazole DR ODT). These data were found to be acceptable and have since been applied to another nonprescription PPI marketed by Dexcel (e.g., NDA 209400, omeprazole DR ODT) as these data apply to comprehension of the melting/dissolving feature of the dosage form (DR ODT). The cover letter dated December 18, 2019 from Dexcel (section 1.2 eCTD dated December 20, 2020) references and includes the submission of this previously submitted label comprehension study report submitted and reviewed during NDA 208025, S-007.

d. The statement of identity (SOI) appears on the left, middle portion of the PDP and states:

"**Esomeprazole**
Delayed Release Orally Disintegrating Tablets 20 mg
Acid Reducer"

Comment: This is acceptable. The proposed SOI meets the regulatory requirements, per 21 CFR 201.61. Additionally, the SOI is consistent with class labeling of nonprescription PPIs in terms of the pharmacologic action being listed as "Acid Reducer" and the USP Salt Policy in terms of the established name.[2] As it relates to the USP Salt Policy, the established name of this drug product is esomeprazole magnesium trihydrate and the salt is not to be used in the established name of new drug products unless the salt provides critical clinical information. The salt does not provide critical clinical information for esomeprazole. Instead, the USP salt policy states that the strength of the active moiety is to be used. For esomeprazole, this is 20 mg, not 22.3 mg. This is consistent with the listed drug for this NDA, esomeprazole delayed-release capsules/NDA 204655/Nexium 24HR®.

e. The statement: "Melts in your mouth Dissolves without water" appears in white font on a red banner below the statement of identity.

Comment: This statement is previously approved in the labeling of other nonprescription PPIs (NDA 209400 and NDA 208025) and is intended to reiterate the dissolving nature of the DR ODT formulation. As in the case with these other NDAs, if the pharmacokinetics data meet the disintegration criteria and receives an approval recommendation from the clinical pharmacology reviewer team, then this statement is acceptable. This will be addressed in an addendum once clinical pharmacology reviews are complete.

[2] **Guidance for Industry Naming of Drug Products Containing Salt Drug Substances (June 2015); accessible at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/naming-drug-products-containing-salt-drug-substances**

f. The declaration of net quantity appears on the left, lower corner of the PDP and states: "**X** TABLETS."

Comment: The "TABLETS**" portion of the declaration of net quantity is reduced in prominence in comparison to the numerical value both in terms of font size and use of boldface type. 21 CFR 201.62(g) states that "The declaration shall appear in conspicuous and easily legible boldface print or type in distinct contrast (by typography, layout, color, embossing, or molding) to other matter on the package; except that a declaration of net quantity blown, embossed, or molded on a glass or plastic surface is permissible when all label information is so formed on the surface."
It is recommended that the declaration of net quantity be revised to increase the conspicuousness and prominence of the "TABLETS" portion of the declaration of net quantity by applying boldface type and increased font size.**

The declaration of net quantity is important information for consumers as it provides consumers truthful and unexaggerated information regarding the contents of a commodity, ultimately providing consumers the ability to make value comparisons. Send an information request to Dexcel with the following note: Increase the prominence of "TABLETS" in the declaration of net quantity by using boldface type, per 21 CFR 201.62(g). Also, increase the font size similar to that of the numerical value in the declaration of net quantity. This information is important for consumers to make fair value comparisons of the contents within products.

g. The following statement appears on the left, lower corner of the PDP, below the declaration of net quantity:

"[One][Two][Three] 14-day course[s] of treatment
May take 1 to 4 days for full effect"

Comment: This is acceptable. Both of these statements are found in the class labeling of nonprescription PPIs. Also, note that the statement "May take 1 to 4 days for full effect" is also found in the DFL (Uses heading, second bullet). This is acceptable.

h. The statement "Wildberry Flavor" encircled with a white line and blue background appears on the right, lower corner of the PDP.

Comment: An information request was sent to Dexcel on April 3, 2020 requesting clarification on the flavor of this product as the NDA submission included documentation of a (b) (4) berry flavor (see section 3.2.P.1, Description and Composition of the Drug Product in the eCTD dated December 20, 2019), yet the labeling contained references to wildberry flavor on the PDP, both in terms of text "Wildberry Flavor" and imagery (i.e.,

image of a cluster of berries including raspberry, blueberry, and blackberry). Dexcel responded on April 9, 2020 by clarifying that the drug product contains the same (b) (4) berry flavor that is found in another marketed product by Dexcel, NDA 22032, omeprazole, 20 mg DR tablets (no proprietary name. Of note, the drug product marketed under NDA 22032, omeprazole, 20 mg DR tablets contains (b) (4) berry with the addition of mint flavor. The NDA 22032 drug product, (b) (4) is marketed as wildberry mint. The wildberry mint flavor was supported by a previously reviewed sensory evaluation survey in which ten study participants described the flavor of the tablet as both berry and mint, with an aftertaste that was more strongly mint than berry. FDA accepted this survey to support the wildberry mint flavor in NDA 22032, S-024 approved March 6, 2015.

In alignment with the previous approval of NDA 22032, S-024 and the sensory evaluation survey suggesting consumers perceived the flavor to be wildberry, it is acceptable for this product to be labeled as wildberry.

i. An image of the drug product (blue tablet with an imprint of "20" placed in the center of the tablet) with white sparkles surrounding the tablet appears on the right, lower corner of the PDP. The statement "Actual size" is placed below the image.

Comment: The image appears to be of actual size, shape, and imprint as verified by "Description and Composition" file in 3.2.P.1 sin the eCTD (submitted on December 20, 2019). This is acceptable.

j. The outer carton contains a white background with a multi-line wave placed on the lower third of the PDP. The wave is turquoise and is filled in with a rich turquoise in the area below the wave on the PDP (14-, 28-, and 42-count outer cartons), as well as the right and left side panels of the outer carton (28- and 42-count outer cartons). Although much of the area under the wave is turquoise, one area has an indigo color (lower, right corner of the PDP) and appears with the image of the tablet.

Comment: This is acceptable.

k. A duplicate SOI (see section II.i.d.) appears on the top panel of the outer carton.

Comment: This aligns with the SOI on the PDP and is acceptable.

l. The tamper-evident feature statement appears on the top panel of the outer carton and states the following: "Safety Feature- Do not use if printed tablet blister unit is open or torn." The statement appears in red font and contained within a red box.

Comment: This complies with 21 CFR 211.132, and therefore, is acceptable.

m. The following statement appears on the top panel of the outer carton: "KEEP THE CARTON AND PACKAGE INSERT. THEY CONTAIN IMPORTANT INFORMATION."

Comment: This is not acceptable, and an information request is necessary. This application does not include a proposed package insert although the statement directs a consumer to a package insert. An information request is needed to clarify for the consumer. Dexcel will need to submit the package insert for review to the NDA as it is labeling, if it is the intention of Dexcel to reference a package insert on the outer carton. Alternatively, the statement may be revised to accurately inform consumers of the labeling that is actually provided to them (i.e., carton alone). It is noted that most marketed nonprescription PPIs do not contain a package insert and instead include the "Tips for Managing Heartburn" on the outer carton. All of the proposed outer carton labeling contains the "Tips for Managing Heartburn" satisfying the need to not include a package insert if Dexcel prefers.

n. A barcode appears on the top panel of the outer carton.

Comment: This is not regulatorily required but is acceptable.

o. The country of origin and manufacturer information appears on the left side panel of the outer carton. The statements read:

"Made in Israel Manufactured by:
Dexcel Pharma Technologies Ltd. 10 Hakidma St. Yokneam 2069200, Israel."

Comment: This complies with 21 CFR 201.1 This is acceptable from an IDS perspective.

p. The "Tips for Managing Heartburn" appear on the bottom panel of the outer carton. In total, the following is present:

"Tips for Managing Heartburn

- ■ Avoid foods or drinks that are more likely to cause heartburn, such as rich, spicy, fatty and fried foods, chocolate, caffeine, alcohol and even some acidic fruits and vegetables.
- ■ Eat slowly and do not eat big meals.
- ■ Do not eat late at night or just before bedtime.
- ■ Do not lie flat or bend over soon after eating.
- ■ Raise the head of your bed.
- ■ Wear loose-fitting clothing around your stomach.
- ■ If you are overweight, lose weight.
- ■ If you smoke, quit smoking."

Comment: This is acceptable. The tips for managing heartburn are class labeling for nonprescription PPIs.

q. A space holder for the Batch number and expiry appear on the right, side panel of the outer carton. The following appear on the right, side panel:
"Batch No
EXP"

Comment: Defer to DEMPA as there is a recommended format for this information. From a nonprescription IDS labeling perspective, this is acceptable.

r. For the 14-count inner carton configuration without an image of a cluster of berries. The statement "**NOT FOR RESALE**" in red font, enclosed within a box appears on the top panel of the outer carton.

Comment: This is acceptable.

ii. Outer Carton Drug Facts Label

a. ***Active ingredient/Purpose***
The following appears in the Active Ingredient heading:

Active ingredient (in each tablet)	Purpose
Esomeprazole 20 mg_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _	Acid reducer
(Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate)	

Comment: The USP Salt policy allows for simplification of the established name of some drug-salt products and applies to this active ingredient as the salt does not provide vital clinical information, which is the case for this active ingredient. An inconsistency is noted in the description of the dosage form. The USP Salt Policy equivalency statement "(Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate)**" references only part of the dosage form, the "delayed-release" component. The incomplete dosage form (DR tablet) happens to also be another dosage form that is distinct from the DR ODT. This partial reference creates an opportunity for confusion.**

An information request is recommended. It is recommended that the complete dosage form be referenced in the USP Salt Policy equivalency statement "(Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate).**" It is recommended that the equivalency statement include the complete dosage form (DR ODT) to maintain a level of consistency with other marketed nonprescription PPIs that apply the USP Salt Policy. For example, the listed drug (esomeprazole delayed-release capsules/NDA 204655/Nexium 24HR®) contains the following equivalency**

statement "(Each delayed-release capsule corresponds to 22.3 mg esomeprazole magnesium trihydrate)." Another marketed nonprescription PPI, esomeprazole delayed-release tablets/NDA 207920/Nexium 24HR®, contains the following equivalency statement "(Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate)." Also, omeprazole magnesium (NDA 21229, Prilosec OTC®) contains the following equivalency statement (equivalent to 20.6 mg omeprazole magnesium) but the description of the equivalency statement within the active ingredient heading content states "Omeprazole delayed-release tablet 20 mg." All of these marketed products express the full dosage form while also applying the USP Salt Policy. It is recommended that Dexcel add the complete dosage form in the equivalency statement, similar to that other marketed nonprescription PPIs.

b. Uses

The following appears in the Uses heading:

- treats frequent heartburn (occurs 2 or more days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

Comment: The Uses heading aligns with the listed drug (esomeprazole delayed-release capsules/NDA 204655/Nexium 24HR®) and the class of nonprescription PPIs. This heading also meets the requirements of 21 CFR 201.66(c)(4). This is acceptable.

c. ***Warnings***

i. Allergy alert

The following statement appears in the Allergy alert subheading:

"Allergy alert: Do not use if you are allergic to esomeprazole"

Comment: The Allergy alert heading aligns with the listed drug (esomeprazole delayed-release capsules/NDA 204655/Nexium 24HR®). This heading also meets the requirements of 21 CFR 201.66(c)(5)(B). This is acceptable.

ii. Do not use

The following bulleted statements appear in the Do not use heading:

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.

Comment: This subheading aligns with the class labeling of nonprescription PPIs, including the listed drug (esomeprazole DR capsules/NDA 204655/Nexium 24HR®). This subheading also aligns with 21 CFR 201.66(c)(5)(H)(iii), except for the application of boldface type to "if you have." 21 CFR 201.66(c)(5)(H)(iii) calls for the subheading "Do not use" to be in boldface type followed by all contraindications for use with the product. However, the boldface type as proposed is aligns with previously approved listed drug, therefore, this is acceptable.

iii. Ask a doctor before use if you have
The following bulleted statements appear in the **Ask a doctor before use if you have** subheading.

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

Comment: This subheading aligns with the class labeling of nonprescription PPIs and 21 CFR 201.66(c)(5)(H)(iv), and therefore, is acceptable.

iv. Ask a doctor or pharmacist before use if you are
The following bulleted statements appear in the **Ask a doctor or pharmacist before use if you are** subheading:

Ask a doctor or pharmacist before use if you are
■ taking a prescription drug. Acid reducers may interact with certain prescription drugs.

Comment: This subheading aligns with the class labeling of nonprescription PPIs and 21 CFR 201.66(c)(5)(H)(v), and therefore, is acceptable.

v. Stop use and ask a doctor if
The following bulleted statements appear in the **Stop use and ask a doctor if** subheading:

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

Comment: This subheading aligns with the class labeling of nonprescription PPIs and 21 CFR 201.66(c)(5)(H)(vii), and therefore, is acceptable.

vi. If pregnant or breast feeding

The following appears in the **If pregnant or breast-feeding** subheading.

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).

Comment: This subheading contains the required text, per 21 CFR 330.1(g) with the addition of the actual Poison Control Center phone number. Providing the Poison Control Center phone number (phone number verified online on May 28, 2020)[3] benefits the consumer by eliminating the need to look anything up in the event that a consumer needs to call Poison Control. This phone number is provided on other approved DFLs (e.g., NDAs 22032, 209400; Dexcel is the sponsor for these NDAs).

d. ***Directions***

The Directions heading contains the following statements:

Directions
■ adults 18 years of age and older
■ this product is to be used once a day (every 24 hours), every day for 14 days
■ may take 1 to 4 days for full effect

14-Day Course of Treatment
■ take 1 tablet before eating in the morning
■ do not crush or chew tablets
■ place the tablet on tongue; tablet disintegrates, with or without water.
The tablets can also be swallowed whole with water.
■ take every day for 14 days
■ do not take more than 1 tablet a day
■ do not use for more than 14 days unless directed by your doctor
■ do not take this medicine with alcohol

[3] https://www.google.com/search?q=poison%20control%20center%20phone%20number&cad=h (Chrome)

Repeated 14-Day Course (if needed)
■ you may repeat a 14-day course every 4 months
■ do not take for more than 14 days or more often than every 4 months unless directed by a doctor

■ children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.

Comment: The directions differ from the listed drug (esomeprazole delayed-release capsules/NDA 204655/Nexium 24HR®) as the listed is not an ODT formulation and therefore, does not include directions to place the tablet on tongue; tablet disintegrates, with or without water, or the option to swallow without water. Additionally, the bulleted statement "do not take this medicine with alcohol" (Directions heading) is not found in the listed drug's DFL. However, the directions for use do align with other nonprescription DR ODT PPI drug products (e.g., NDAs 208025 and 209400). Clinical pharmacology experts reviewed the submitted bioequivalence study (Study 190030) assessing elements that impact directions to take the drug product with or without water; and the in vitro alcohol dose dumping study (Section 3.4 in Module 2.7.1). If the clinical pharmacology team provides an approval recommendation, then this heading would be acceptable. This will be addressed in an addendum once clinical pharmacology reviews are complete. The IDS labeling reviewer's comment on this labeling element is deferred to an upcoming addendum.

e. Other Sections/Issues

i. The Other Information heading appears with the following bulleted statements:

Other Information
■ read the directions and warnings before use
■ keep the carton. It contains important information.
■ store at 20-25°C (68-77°F); store in the original package

Comment: This is not acceptable. Information about protecting this drug product from high heat and moisture is missing. CMC confirmed that this information applies to this product. This statement is recommended for consistency among similar products and usefulness in maintaining nonprescription drug products. It is noted that the two other DR ODT nonprescription PPIs on the market (NDA 208025 and NDA 209400; Dexcel is also the sponsor) provides information in the DFL to keep these DR ODT drug products out of high heat and moisture.

ii. The DFL meets the format specifications outlined in 21 CFR 201.66.

Comment: This is acceptable.

f. Inactive ingredients

The following text is proposed in the Inactive Ingredients heading:

"***Inactive ingredients*** acetone, alcohol, amino methacrylate copolymer, ascorbic acid, benzyl alcohol, cetyl alcohol, colloidal silicon dioxide, crospovidone, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, flavor, hypromellose, hypromellose phthalate, isopropyl alcohol, mannitol, microcrystalline cellulose, modified starch, polysorbate 80, pregelatinized starch, silicon dioxide, sodium stearate, sodium stearyl fumarate, sorbitol, sucralose, sugar spheres, talc, titanium dioxide, triacetin, triethyl citrate"

Comment: This complies with 21 CFR 201.66(c)((8). This is acceptable from an IDS perspective. Confer with Chemistry, Manufacturing and Controls reviews for acceptability from this perspective.

iii. Immediate Container Label

2- and 7-count immediate container (blister pack) labels

a. A duplicate SOI appears on the top of each blister unit that contains a tablet.

Comment: This is acceptable.

b. The manufacture's name and address appear below the SOI on each blister unit containing a tablet. The specific text:

Dexcel Pharma Technologies Ltd.
10 Hakidma Street,
Yokneam 2069200, Israel

Comment: This is acceptable from an IDS perspective.

c. Directions on how to extract the tablet from the blister unit appears on each blister unit containing a tablet. The specific text is enclosed within a box state:

1. SEPARATE AT PERFORATION. 2. PEEL AT ARROW.

Additionally, the statement "PEEL" and an arrow appears in the bottom right or left corner of each blister unit containing a tablet.

Comment: This is consistent with Dexcel's other approved products contained within a blister package (NDA 22032, 209400, 208025) and

applies to the proposed drug product under review (NDA 214278). This is acceptable.

d. The batch and expiry information appear on each blister unit containing a tablet running down each unit. The specific text includes:

"00000000 EXP MMYY"

Comment: See DEMPA review for recommendation for a labeling change.

e. An empty blister unit in the lower, left corner of the blister pack contains abbreviated directions. The abbreviated directions state:

Place tablet on tongue; tablet disintegrates, with or without water. Do not crush or chew tablets. One 14-day course of treatment. Take 1 tablet every day for 14 days. Do not take for more than 14 days or more often than every 4 months unless directed by a doctor.

Comment: The directions differ from the listed drug (esomeprazole delayed-release capsules/NDA 204655/Nexium 24HR®) as the listed is not an ODT formulation and therefore, does not include directions to place the tablet on tongue; tablet disintegrates, with or without water, or the option to swallow without water. However, the directions for use do align with other nonprescription DR ODT drug products (e.g., NDAs 208025 and 209400). Clinical pharmacology experts reviewed the submitted bioequivalence study (Study 190030) assessing elements that impact directions to take the drug product with or without water. If the clinical pharmacology team provides an approval recommendation, then this heading would be acceptable. This will be addressed in an addendum once clinical pharmacology reviews are complete.

iv. Consumer Information Leaflet or Package Insert

This NDA submission does not include a consumer information leaflet or package insert. Similar to other marketed nonprescription PPIs (e.g., NDA 209400, 21229, 204655, etc.), a consumer information leaflet or package insert is not included within packaged drug products. It has become class labeling to include the tips for managing heartburn on the outer carton labeling if the consumer information leaflet or package insert is not included with the marketed product. The tips for managing heartburn were previously outlined in the consumer information leaflet. FDA finds this information to be important information and beneficial to consumers who self-treat

with a nonprescription PPI. This original NDA includes the tips for managing heartburn on the outer carton.

Comment: This is acceptable. See reviewer's comments about the reference to a package insert on the top panel in section II.A.i.m.

B. 2-count outer cartons without an image of a berry cluster.
See sections II.A.i-iv, except item g.

i. Outer Carton Label Outside Drug Facts Label

a. The statement "FREE SAMPLE" appears in red boldface type in the upper, right corner of the PDP.

Comment: The 2-count configuration is considered a sample for the class of nonprescription PPIs. This is acceptable.

b. The statement "Follow samples with a 14-day course of treatment" is added to underneath the declaration of net quantity. The statement appears in navy blue boldface type.

Comment: This is not acceptable, and an information request is necessary. The previously approved statement on sample configuration for the listed drug for this NDA (esomeprazole DR capsules/NDA 204655/Nexium 24HR®) contains a more informative statement: "First 2 doses of a 14-day course of treatment" and is located underneath the declaration of net quantity on the PDP. It is recommended that the statement "First 2 doses of a 14-day course of treatment" replace the proposed statement "Follow samples with a 14-day course of treatment" to provide clarity to consumers on how the two sample doses fit into the set treatment course.

c. The statement "May take 1 to 4 days for full effect" is missing from the PDP.

Comment: This is not acceptable, and an information request is necessary. All other outer cartons contain this statement on the PDP. Statements such as "24HR" and "24 Hour" statements are acceptable on currently marketed nonprescription PPI labels when the statement "May take 1 to 4 days for full effect" is also present on the PDP (recent precedent NDA 22032, S-041, approved on April 8, 2019). The product is taken once every 24 hours and the accompanying statement "May take 1 to 4 days for full effect" is intended to inform consumers about the expectation of heartburn relief starting to take effect in 1 to 4 days. The PDP contains "24h" and needs the accompanying statement "May take 1 to 4 days for full effect." Send an information request to Decxel recommending the addition of "May take 1 to 4 days for full effect" to the PDP of the sample outer cartons. See this reviewer's comments about use of "24h" in section II.A.i.b. Note, the Division of Medication Error Prevention and Analysis review aligns with IDS with this recommendation.

d. The statement "NOT FOR SALE" appears in red boldface type enclosed within a red box on the top panel of the outer carton.

Comment: This statement associates with the sample and is acceptable.

C. 2-, 14-, 28-, and 42-count outer cartons with an image of a berry cluster.
See sections II.A.i-iv and II.B.

i. Outer Carton Label Outside Drug Facts Label
An image of image of a cluster of berries including raspberry, blueberry, and blackberry is placed lower, right corner of the PDP. This image is adjacent to the text "Wildberry Flavor."

Comment: This image appears on half of the proposed labels; the other half only contain the text referencing the wildberry flavor. See II.A.i.h for reviewer's finding of acceptability of the flavor. This is acceptable.

C. 2-count outer carton with an image of a berry cluster.
See sections II.A- C.

III. RECOMMENDATIONS

Issue an **INFORMATION REQUEST** letter to the sponsor for the submitted esomeprazole delayed-release orally disintegrating tablets labeling and request the following revisions.

All outer carton labeling:

1. We note the following statement appears on the top panel of the proposed outer carton labeling: "KEEP THE CARTON AND PACKAGE INSERT. THEY CONTAIN IMPORTANT INFORMATION." Submit the package insert for review or delete reference to the package insert in this statement.
2. We note that "24h" appears on the principal display panel (PDP) adjacent to the "Treats **Frequent** Heartburn!" flag. We recommend using either "24 hr" or "24 hour" (capitalization preference is deferred to Dexcel) to clearly communicate the once every 24 hours administration of this drug product.
3. We note that "TABLETS" in the declaration of net quantity is reduced in prominence in comparison to the numerical value both in terms of font size and use of boldface type. Increase the prominence of "TABLETS" in the declaration of net quantity by using boldface type, per 21 CFR 201.62(g). Also, increase the font size similar to that of the numerical value in the declaration of net quantity. This information is important for consumers to make fair value comparisons of the contents within products.
4. We note the Active ingredient heading in the Drug Facts label contains the equivalency statement "(Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate)." The "delayed-release tablet" references only part of the dosage form of this drug product. We recommend using "delayed-release orally disintegrating tablet" to maintain a level of consistency with other marketed nonprescription PPIs that apply the USP Salt Policy.
5. The Other information heading does not contain a statement advising consumers to keep this product out of high heat and moisture consistent with your other marketed nonprescription delayed-release orally disintegrating tablet PPIs (NDAs 208025 and 209400). Add the statement "keep product out of high heat and moisture" to the Other information heading. This is useful information for consumers to keep in mind to maintain the integrity of the drug product.

2- count outer carton labeling:

6. We note that all outer carton labeling contains the statement "May take 1 to 4 days for full effect" on the PDP except for the 2-count sample outer carton labeling components. Statements such as "24HR" and "24 Hour" statements are acceptable on currently marketed nonprescription PPI labeling when the statement "May take 1 to 4 days for full effect" is also present on the PDP. The product is taken once every 24 hours and the accompanying statement "May take 1 to 4 days for full effect" is intended to inform consumers about the expectation of heartburn relief starting to take effect in 1 to 4 days. Add the statement "May take 1 to 4 days for full effect" to the 2-count outer cartons.
7. We note the statement "Follow samples with a 14-day course of treatment" is proposed underneath the declaration of net quantity on the 2-count sample outer cartons. The previously approved statement on the sample outer cartons of the listed drug for this NDA (esomeprazole delayed-release capsules/NDA 204655/Nexium 24HR®) contain a

more informative statement “First 2 doses of a 14-day course of treatment” and is located underneath the declaration of net quantity on the PDP. It is recommended that the statement “First 2 doses of a 14-day course of treatment” be utilized to provide clarity to consumers on how the sample doses fit into the set treatment course.

Other:

8. See recommendation DMEPA for batch and exp display.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LORI N PARSONS
08/31/2020 05:55:19 PM

KEVIN L LORICK
09/01/2020 07:38:57 AM
I concur with the review and recommendations.

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

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

Date of This Review:	May 26, 2020
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPD I)
Application Type and Number:	NDA 214278
Product Name, Dosage Form, and Strength:	Esomeprazole Delayed-Release Orally Disintegrating Tablets, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Over-the-Counter (OTC)
Applicant/Sponsor Name:	Dexel Pharma Technologies LTD
FDA Received Date:	December 20, 2019
OSE RCM #:	2020-829
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Associate Director for Nomenclature and Labeling:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the review process for NDA 214278, the Division of Nonprescription Drugs I (DNPD I) requested that we review the proposed esomeprazole delayed-release orally disintegrating tablets container labels and carton labeling for areas of vulnerability that may lead to medication errors.

Dexel Pharma Technologies LTD (Dexel) is seeking approval under a 505(b)(2) application relying on the listed drug (LD) Nexium 24HR (NDA 204655).

Of note, the Applicant plans to market this proposed product with the established name.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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

3 FINDINGS OF THE MATERIALS REVIEWED

We reviewed the proposed esomeprazole delayed-release orally disintegrating tablets blister container labels and note that partial instructions on how to take the product, to separate and open the product appear on the blister container labels. These same partial instructions also appear on Dexel's currently marketed acid reducing products (i.e., lansoprazole and omeprazole delayed release orally disintegrating tablets). We are unaware of any postmarketing medication errors related to these partial instructions on the blister container labels for Dexel's currently marketed acid reducing products. Thus, we do not find reason for revision or objection at this time.

We find that the proposed esomeprazole delayed-release orally disintegrating tablets container labels and carton labeling may be improved for clarity to ensure safe use of the product and to minimize potential medication errors. Our recommendations are provided in Section 4.

4 RECOMMENDATIONS FOR DEXEL PHARMA TECHNOLOGIES LTD

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels & Carton Labeling

1. The container labels and carton labeling contain a placeholder for the lot number and expiration date and as currently presented and the format for the expiration date is not defined in the carton labeling. Therefore, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use throughout your blister container labels and carton labeling. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2. Additionally, the header "Batch No." appears on the carton labeling but not on the blister container labels. Therefore, for consistency, include the header "Batch No." to the blister container labels.

B. Carton Labeling

1. Revise the graphic image "24h" so that it reads "24hr" or "24 Hour" to clearly represent the duration of use (every 24 hours). We note that Dexel's other acid reducing products (i.e., lansoprazole and omeprazole delayed release orally disintegrating tablets) also use either the term "24HR" or "24 Hour."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Esomeprazole Delayed-Release Orally Disintegrating Tablets received on December 20, 2019 from Dexel Pharma Technologies LTD, and the listed drug (LD).

Table 2. Relevant Product Information for Esomeprazole Delayed-Release Orally Disintegrating Tablets and the Listed Drug		
Product Name	Esomeprazole Delayed-Release Orally Disintegrating Tablets	Nexium 24HR[a]
Initial Approval Date	N/A	3/28/2014
Active Ingredient	Esomeprazole	Esomeprazole
Indication	Drug Facts Label (DFL) *Uses*: ***Uses*** ■ treats frequent heartburn (occurs **2 or more** days a week) ■ not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect	DFL *Uses*: ***Uses*** ■ treats frequent heartburn (occurs **2 or more** days a week) ■ not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect
Route of Administration	Oral	Oral
Dosage Form	Delayed-release orally disintegrating tablets	Capsules
Strength	20 mg	20 mg

[a] Nexium 24HR [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 APR 04. Supplement-11. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204655Orig1s011lbl.pdf.

Dose and Frequency	DFL *Directions*: ***Directions*** ■ adults 18 years of age and older ■ this product is to be used once a day (every 24 hours), every day for 14 days ■ may take 1 to 4 days for full effect **14-Day Course of Treatment** ■ take 1 tablet before eating in the morning ■ **do not crush or chew tablets** ■ place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water. ■ take every day for 14 days ■ do not take more than 1 tablet a day ■ do not use for more than 14 days unless directed by your doctor ■ do not take this medicine with alcohol **Repeated 14-Day Course (if needed)** ■ you may repeat a 14-day course every 4 months ■ **do not take for more than 14 days or more often than every 4 months unless directed by a doctor** ■ children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.	DFL *Directions*: ***Directions*** ■ adults 18 years of age and older ■ this product is to be used once a day (every 24 hours), every day for 14 days ■ may take 1 to 4 days for full effect **14-Day Course of Treatment** ■ swallow 1 capsule with a glass of water before eating in the morning ■ take every day for 14 days ■ do not take more than 1 capsule a day ■ swallow whole. Do not crush or chew capsules. ■ do not use for more than 14 days unless directed by your doctor **Repeated 14-Day Courses (if needed)** ■ you may repeat a 14-day course every 4 months ■ **do not take for more than 14 days or more often than every 4 months unless directed by a doctor** ■ children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.
How Supplied	• 2-count blister sample container in a carton • 7-count blister container • 14-count (two 7-count blisters in a carton) • 28-count (four 7-count blisters in a carton) • 42-count (six 7-count blisters in a carton)	• 2-count sample bottle • 14-count bottle • 28-count (two 14-count bottles in a carton) • 42-count (three 14-count bottles in a carton)
Storage	Store at 20-25°C (68-77°F)	Store at 20-25°C (68-77°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Esomeprazole Delayed-Release Orally Disintegrating Tablets labels and labeling submitted by Dexel Pharma Technologies LTD.

- Container label received on December 20, 2019
- Carton labeling received on December 20, 2019

G.2 Label and Labeling Images

Container Labels:

(b) (4)

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GRACE JONES
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