CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214278Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 214278
Review # 1

Drug Name/Dosage Form	Esomeprazole magnesium DR ODT (Esomeprazole)
Strength	Delayed release orally disintegrating tablets 20 mg
Route of Administration	Oral
Rx / OTC Dispensed	OTC
Applicant	Dexcel Pharma Technologies LTD
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	20-December-2019	All
Response to quality IR	27-Feb-2020(E-mail)	ONDP (Biopharm)
Response to quality IR	19-Mar-2020	ONDP (Drug substance & Drug product)
Response to quality IR	12-May-2020	ONDP/DNDPIII (Drug product)
Response to quality IR	02-April-2020	ONDP (Biopharm)
Response to quality IR	20 -April-2020	ONDP/DNDPIII (Drug product)/OPMA (Process & facility)
Response to quality IR	01-June-2020	ONDP/DNDPIII (Drug product)

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus, Ph.D.	ONDP/NDAPI-II/ Branch III
Drug Product	Christopher Galliford, Ph.D.	ONDP/DNDP-III/ Branch VI
Process & facility	Shu-Wei Yang, Ph.D.	OPF/DPAII/Branch VI
Biopharmaceutics	Rajesh Savkur, Ph.D.	NA
Regulatory Business Process Manager	Teshara Bouie	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-III/ Branch VI
Laboratory (OTR)	NA	NA
Environmental Assessment (EA) and Labeling	Christopher Galliford, Ph.D.	ONDP/DNDP-III/ Branch VI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs/MAF:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Esomeprazole Magnesium	1	Adequate	3/25/2020	None
	III		(b) (4)	4	Adequate		None
	III			4	Adequate		None
	IV			4	Adequate		None
	IV			4	Adequate		None

C. [1] Action codes for DMF Table:
D. 1 – DMF Reviewed.
E. Other codes indicate why the DMF was not reviewed, as follows:
F. 2 –Type 1 DMF
G. 3 – Reviewed previously and no revision since last review
H. 4 – Sufficient information in application
I. 5 – Authority to reference not granted
J. 6 – DMF not available
K. 7 – Other (explain under "Comments")

L. [2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	129881	Esomeprazole delayed release orally disintegrating tablets
PIND/PNDA	129881	Esomeprazole delayed release orally disintegrating tablets, 20 mg

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Office of Surveillance	NA			

Table of Contents

(Other reviews are in IQA submitted in DARRTS)

Executive Summary (NDA-214278)

I. Recommendations

Regarding Chemistry Manufacturing and Controls, the application may be approved.

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the submitted application the drug substance, drug product, biopharmaceutics, process and facility sections are reviewed and found adequate to support the approval of the application (see attached reviews). The drug product is granted a 24-month shelf life when stored at controlled room temperature.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments:

The proposed '-Esomeprazole Delayed-Release orally disintegrating tablet (ODT)' is developed by Dexcel Pharma Technologies (DPT), utilizing the 505(b)(2) regulatory pathway. The Sponsor intends to rely upon the Agency's prior findings of safety and efficacy for the reference listed drug (RLD), Nexium 24HR OTC (esomeprazole; AstraZeneca LP, NDA 204655). The proposed indication is the treatment of frequent heartburn.
Esomeprazole is the S-isomer of omeprazole and is a member of the proton-pump inhibitor (PPI) class of drugs, which increase intragastric pH, relieving the symptoms of acid-related disorders, including heartburn. Esomeprazole works by inactivating the final step of the gastric acid secretion pathway in gastric parietal cells with a dose-dependent response.
Esomeprazole DR ODT 20 mg contains the active ingredient esomeprazole, which is classified as Biopharmaceutical Classification System (BCS) Class III and is rapidly degraded in acidic condition and is soluble in aqueous solution. Formulation development focused on achieving a tablet comprising delayed-release (b) (4) pellets, together with external excipients enabling oral disintegration of the tablets. Drug substance information is referred to DMF (b) (4). Drug substance DMF (# (b) (4)) and the drug substance information within the application are reviewed by drug substance reviewer on 03/25/2020 and 04/01/2020 respectively. Biopharmaceutics and manufacturing & facility reviews are completed respectively on 07/10/2020 and 05/22/2020. Drug product review includes assessment of environmental analysis and CMC related labeling and package insert are completed on 08/25/2020. All reviews concluded that adequate information is provided to support NDA 214278.
The proprietary name 'Esomeprazole Delayed Release Orally Disintegrating Tablets' is found acceptable by DMEPA.

A. Drug Product Quality Summary

1. Strength: Esomeprazole Delayed Release Orally Disintegrating Tablets 20 mg

2. Description/Commercial Image:

Esomeprazole Delayed Release Orally Disintegrating Tablets 20 mg are round bluish mottled uncoated tablets, debossed "20" on one side. The tablets are packaged in 7- count Aluminum (b) (4) blisters. Each pack contains two blisters (a total of 14 tablets) for one 14 days course of treatment. The Orally Disintegrating Tablet (ODT) is comprised of coated pellets containing the active substance, Esomeprazole Magnesium Trihydrate, mixed with excipients to form a tablet which disintegrates when placed on the tongue. The formulation contains a single active ingredient, esomeprazole 20 mg (esomeprazole magnesium trihydrate 22.27 mg). Inactive ingredients include: 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.
Although no novel excipients are used in the manufacture of or are present in the drug product, (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 was found acceptable (see drug product review). Drug product formulation also contain two other non-compendial 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 is provided in the application and manufacturing detail is referred to DMF (b) (4). Both (b) (4) and the (b) (4) berry flavor information was found acceptable (see DP review). It is found that the delayed-release enteric coating (b) (4) is identical to that found in the applicant's previously approved omeprazole delayed release, orally disintegrating tablet formulation (NDA 209400, granted approval in July 2017). It is noted that the key quality attributes pertaining to the integrity of the enteric coating (gastric résistance) and oral disintegration are well controlled. This is relevant because the key difference between this formulation and the reference listed drug Nexium® is the type of delayed release oral formulation, i.e. capsule versus orally disintegrating tablet. One of the critical quality attributes, disintegration specifications at release (proposed (b) (4) sec) and stability (proposed (b) (4) sec) was an issue during the drug product review and it was resolved with multiple information request with same acceptance criterion of (b) (4) sec at both release and stability.

3. Summary of Product Design

Esomeprazole Delayed-Release Orally Disintegrating Tablets, 20 mg are round bluish mottled uncoated tablet; debossed "20" on one side. The Orally Disintegrating Tablet (ODT) is comprised of coated pellets containing the active substance, esomeprazole, mixed with excipients to form a tablet which disintegrates when placed on the tongue.

4. List of Excipients:

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.

5. Process Selection (Unit Operations Summary)

(b) (4)

6. **Container Closure**:

The sponsor has provided comprehensive information about the container closure system. The Esomeprazole Delayed-Release Orally Disintegrating Tablets, 20 mg will be packed in the following primary packaging: Alu-Alu blister comprised of aluminum laminate base foil and lidding foil. Each blister will contain 7 tablets. Esomeprazole Delayed-Release Orally Disintegrating Tablets are available in 14, 28 and 42 blister cartons, for one, two and three courses of treatment. Each pack for one course of treatment contains 14 tablets. All components used in packaging have been previously used in FDA approved product (Omeprazole DR Orally Disintegrating Tablets, NDA 209400). The suppliers for each component, DMF number and letter of authorization are provided in the application.

7. Expiration Date & Storage Conditions

The drug product is granted a 24-month shelf life when stored at 25ºC/40%RH.
The storage statement will be written as "Store (b) (4) 20ºC – 25ºC (68ºF - 77ºF). This reflects the numerical value of the controlled room temperature [stored at 25ºC (77ºF) with excursions permitted to 15ºC-30ºC (59ºF-86ºF)].

8. List of co-packaged components: None

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	

Non Proprietary Name of the Drug Product	Esomeprazole Delayed-Release Orally Disintegrating Tablets
Non Proprietary Name of the Drug Substance	Esomeprazole
Proposed Indication(s) including Intended Patient Population	the treatment of frequent heartburn (occurring at least twice a week) in adult (18 years and above)
Duration of Treatment	14 days
Maximum Daily Dose	N/A
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification: BCS Class III.
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies (For NDA only)
   - Biowaiver Requests: No
   - PK studies: Yes
   - IVIVC: No

D. Novel Approaches

E. Any Special Product Quality Labeling Recommendations
Established name of the drug product:
Esomeprazole

F. Life Cycle Knowledge Information (see table below)

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	2	3	2	12	Controlled with specifications
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on stability data provided

Disintegration	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	2	18	Controlled at release and during stability
Microbial Limits	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	2	2	2	8	Controlled with specifications.

Life Cycle Knowledge Information related to Post-Approval Changes: None

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OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Regarding Chemistry Manufacturing and Controls, the application may be approved.

Application Technical Lead Signature:

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I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

The package insert is a user's guide in the form of a booklet. The drug product is an OTC product and will bear a Drug Facts Label (DFL).

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Esomeprazole Delayed Release Orally Disintegrating Tablets 20 mg.	**Adequate**
Dosage form, route of administration	Oral.	
Controlled drug substance symbol (if applicable)	Not required.	**Adequate**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	20 mg orally disintegrating tablet.	**Adequate**

Conclusion: Adequate

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

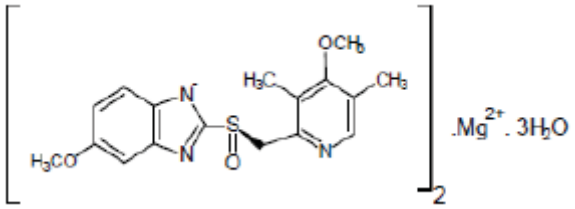
Esomeprazole delayed release, orally disintegrating tablets, 20 mg.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Orally disintegrating tablets.	**Adequate**
Strengths: in metric system	20 mg.	**Adequate**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Esomeprazole Delayed Release Orally Disintegrating Tablets 20 mg are round bluish mottled uncoated tablets, debossed "20" on one side. The tablets are packaged in 7- count Aluminium-Aluminium (b) (4) blisters. Each pack contains two blisters (a total of 14 tablets) for one 14 days course of treatment.	**Adequate**

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

Esomeprazole Delayed Release Orally Disintegrating Tablets 20 mg are round bluish mottled uncoated tablets, debossed "20" on one side. The tablets are packaged in 7- count Aluminium-Aluminium (b) (4) blisters. Each pack contains two blisters (a total of 14 tablets) for one 14 days course of treatment. The Orally Disintegrating Tablet (ODT) is comprised of coated pellets containing the active substance, Esomeprazole Magnesium Trihydrate, mixed with excipients to form a tablet which disintegrates when placed on the tongue.



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.

Item		Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Provided.	**Adequate**
Dosage form and route of administration		Provided.	**Adequate**
Active moiety expression of strength with equivalence statement for salt (if applicable)		Provided.	**Adequate**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		Provided.	**Adequate**
Statement of being sterile (if applicable)		Not required.	**Adequate**
Pharmacological/ therapeutic class		Provided.	**Adequate**
Chemical name, structural formula, molecular weight		Provided.	**Adequate**
If radioactive, statement of important nuclear characteristics.		Not required.	**Adequate**
Other important chemical or physical properties (such as pKa, solubility, or pH)		Provided.	**Adequate**

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Store at 20-25°C (68-77°F); store in the original package.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Esomeprazole 20 mg.	**Adequate**
Available units (e.g., bottles of 100 tablets)	Blister packs of 14, 28 or 42 tablets.	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided.	**Adequate**
Special handling (e.g., protect from light, do not freeze)	Provided.	**Adequate**
Storage conditions	Provided.	**Adequate**

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Dexcel Technologies Inc.	**Adequate**

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

The drug product is packaged in a carton containing blister packs. See next section for sample carton graphics.

Reviewer's Assessment: **Adequate.**

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Esomeprazole Delayed Release Orally Disintegrating Tablets 20 mg	**Adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Esomeprazole 20 mg.	**Adequate**
Route of administration 21.CFR 201.100(b)(3))	Orally disintegrating tablet.	**Adequate**
Net contents* (21 CFR 201.51(a))	14, 28 or 42 tablets.	**Adequate**
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Name of inactive ingredients provided Quantitative composition not required for an oral dosage form	**Adequate**
Lot number per 21 CFR 201.18	Space is provided	**Adequate**
Expiration date per 21 CFR 201.17	Space is provided	**Adequate**
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	**Adequate**
Storage (not required)	Provided	**Adequate**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	**Adequate**
Bar Code per 21 CFR 201.25(c)(2)***	Provided	**Adequate**
Name of manufacturer/distributor (21 CFR 201.1)	Provided	**Adequate**
Warnings	Store at 20 - 25°C (68 - 77°F). Store in original packaging.	**Adequate**

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate.

2) Carton Labeling

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Esomeprazole Delayed Release Orally Disintegrating Tablets 20 mg.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	20 mg.	Adequate
Net contents (21 CFR 201.51(a))	14, 24 or 42 tablets.	Adequate
Lot number per 21 CFR 201.18	Space is provided.	Adequate
Expiration date per 21 CFR 201.17	Space is provided.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ngredient information is required or injectables)[201.10(a), 21CFR201.100(d)(2)]	Not required for an oral dosage form.	Adequate
Sterility Information (if applicable)	Space is provided.	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided.	Adequate
Storage Conditions	Provided.	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all abels or labeling), also see 21 CFR 207.35(b)(3)	Provided.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided.	Adequate
Name of manufacturer/distributor	Provided.	Adequate
"See package insert for dosage nformation" (21 CFR 201.55)	Provided.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Not included.	Adequate
Route of Administration (not equired for oral, 21 CFR 201.100(d)(1) and (d)(2))	Not required.	Adequate

Conclusion: Adequate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
ADEQUATE
Chris Galliford, Ph.D., 8/25/2020

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

Danae Christodoulou, Ph.D., 8/25/2020

Christopher Galliford

Digitally signed by Christopher Galliford
Date: 8/26/2020 09:51:46PM
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Comments: pdf version of review that did not archive properly.

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 8/26/2020 11:02:48PM
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