CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209400Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	209400
Supporting document/s:	1
Applicant's letter date:	6 September 2016
CDER stamp date:	6 September 2016
Product:	Omeprazole DR ODT
Indication:	Frequent heartburn
Applicant:	Dexcel Pharma Technologies, Ltd., Israel Jeanne M. Novak, PhD, Agent CBR International Corp. 2905 Wilderness Place, Suite 202 Boulder, CO 80301
Review Division:	Nonprescription Drug Products
Reviewer:	D. Charles Thompson, RPh, PhD, DABT
Team Leader:	Jane J. Sohn, PhD
Division Director:	Theresa Michele, MD
Project Manager:	Alina Salvatore, RPh, MS, RAC

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209400 are owned by Dexcel Pharma Technologies or are data for which Dexcel Pharma Technologies has obtained a written right of reference. Any information or data necessary for approval of 209400 that Dexcel Pharma Technologies does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 209400.

Reference ID: 4095233

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1 Executive Summary

1.1 Introduction

This application is a 505(b)(2) NDA proposing market registration for a delayed-release orally disintegrating tablet formulation of omeprazole for use in the OTC treatment of frequent heartburn in adults 18 years of age and older. The Sponsor is relying on FDA's previous findings of safety and effectiveness under NDA 021229 (Prilosec OTC, the listed drug).

1.2 Brief Discussion of Nonclinical Findings

No original nonclinical data were included in the application.

1.3 Recommendations

1.3.1 Approvability: Approvable

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: N/A

2 Drug Information

2.1 Drug

CAS Registry Number: 73590-58-6

Generic Name: Omeprazole

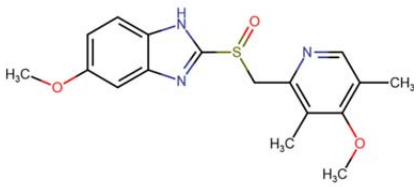
Code Name: N/A

Chemical Name: 5-Methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridyl)methyl)sulfinyl) benzimidazole

Molecular Formula/Molecular Weight: $C_{17}H_{19}N_3O_3S$/345.42 (b) (4)

Reference ID: 4095233

Structure:



Pharmacologic Class: Proton pump inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 021229 (Prilosec OTC, the listed drug); PIND 127169

2.3 Drug Formulation

The proposed drug product is a delayed-release orally disintegrating tablet (DR ODT) formulation of omeprazole, the composition of which is described in the Sponsor's Tables 1, 2, 3, and 4 below.

Table 1 Unit Composition of the (b) (4)

Ingredient	Weight per tablet (mg)	Function	Quality Standard
(b) (4)	(b) (4)		
Sugar Spheres		(b) (4)	NF
(b) (4)			
Omeprazole	20.00		USP
Sodium Stearate	(b) (4)		NF
(b) (4)			USP
			USP
			USP
Mannitol			USP
Talc			USP
(b) (4)			USP
Hypromellose Phthalate (b) (4)			NF
Cetyl Alcohol			NF
Triethyl Citrate			NF
(b) (4)			USP
Titanium Dioxide			USP
(b) (4			NF
			USP
Amino Methacrylate Copolymer			NF
Colloidal Silicon Dioxide			NF
Ferric oxide			NF
(b) (4)			
			USP
			(b) (4)
(b) (4)	(b) (4)	--	--
(b) (4)		(b) (4)	DMF holder standard
Microcrystalline Cellulose			NF
Crospovidone			NF
Sucralose			NF
Ascorbic Acid			USP
Strawberry flavor mixture			DMF holder standard
(b) (4)			NF
Sodium Stearyl Fumarate			NF
(b) (4)			NF
Total tablet weight	336.00		

DR=delayed-release, ODT=orally disintegrating tablet, mg=milligrams, NF=National Formulary, USP=United States Pharmacopeia, DMF=drug master file

2.4 Comments on Novel Excipients

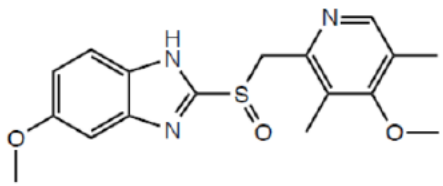
The proposed drug product formulation contains no novel excipients. All proposed excipients and/or excipient mixture components are present at in-product use levels that are at or below previously approved use levels for ODT and/or solid oral dosage forms according to current FDA IID reporting, with the exception of ascorbic acid.

Ascorbic acid (Vitamin C) is proposed for use at a level ((b) (4) mg/tablet) that is slightly higher than is reported for a previously approved ODT dosage form ((b) (4) mg/tablet). The Sponsor submitted a literature-based risk assessment in support of the safety of this slight increase in daily ascorbic acid intake, which is considered to be adequate. The proposed increase does not raise safety concerns and is acceptable.

2.5 Comments on Impurities/Degradants of Concern

All specifications for drug substance impurities are at or below the ICH Q3A-prescribed qualification threshold of NMT 0.15% and are consistent with those specified in the current USP monograph for omeprazole. This includes a specification for (b) (4) (b) (4)) (see Sponsor's structural figures below) of NMT (b) (4) %. Similarly, all drug product impurity specifications are at or below the ICH Q3B-prescribed QT of NMT 0.5%, again including a specification for (b) (4) of NMT (b) (4) %. Nevertheless, the Sponsor has included an 11-page risk assessment document in support of qualification of (b) (4) in the proposed DP at a level of NMT (b) (4) % and has requested "...an opinion on the safety" of this impurity specification.

Figure 1: Structures of Omeprazole and [redacted]



Omeprazole
Chemical Formula: $C_{17}H_{19}N_3O_3S$
Molecular Weight: 345.42

The Sponsor's [redacted] risk assessment document discusses published literature in noting that [redacted] is a circulating [redacted] of omeprazole in both laboratory animals and humans [redacted] Furthermore, [redacted] "...is found at lower concentrations in the human as compared to laboratory animals." These facts, in conjunction with the proposed [redacted] specification limit (i.e., NMT [redacted]%), weigh in favor of a determination that the proposed specification does not raise safety concerns and is, thus, qualified. However, given the Sponsor's request for a safety opinion, a consult on the [redacted] structure was submitted to the CDER Computational Toxicology Team (CDER/OTS/OCP/DARS) to rule out the existence of any potential structural alerts for genotoxicity. It was determined that, "Based on the entire weight of evidence, [redacted] is predicted to be negative for bacterial mutagenicity (CDER/OTS/OCP/DARS, 2017)." Thus, justification for the proposed DP specification for [redacted] of NMT [redacted]% is considered adequate and acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

Omeprazole DR ODT is proposed for use in adults 18 years of age and older in the OTC treatment of frequent heartburn with a recommended dosing regimen of 20 mg (1 tablet) per day for 14 days. If needed, this treatment regimen may be repeated as often as every 4 months.

2.7 Regulatory Background

This is an original 505(b)(2) NDA. A Pre-NDA meeting was held with the Sponsor (under PIND 127169) on 9 May 2016, during which FDA advised that, "You may rely on the FDA's previous findings of safety for the nonclinical portion of your NDA. The adequacy of any additional information provided with the NDA in support of the use of ascorbic acid as an excipient will be a matter of review."

3 Studies Submitted

No nonclinical studies were included in the submission; a 29-page document entitled, "Safety Evaluation of Ascorbic Acid" was provided.

3.1 Studies Reviewed

N/A

3.3 Previous Reviews Referenced

- NDA 021229: Supervisory Pharmacologist Memorandum, Jasti B. Choudary, Ph.D., 14 September 2000.
- NDA 021229: Pharmacology Review, Timothy W. Robison, Ph.D., 12 September 2000.
- NDA 209400: CDER/OTS/OCP/DARS Memorandum: QSAR Consultation on [redacted] (b) (4) 18 January 2017.

11 Integrated Summary and Safety Evaluation

Omeprazole (Prilosec, AstraZeneca Pharmaceuticals) was originally approved as an NME prescription drug product (oral capsule, delayed-release pellets) under NDA 019810 on 14 September 1989. Omeprazole was first approved for OTC use as the magnesium salt under NDA 021229 on 20 June 2003 (Prilosec OTC, AstraZeneca Pharmaceuticals). Nonclinical safety support for this application relied largely on cross reference to the original Rx NDA, though substantial additional nonclinical studies were required to support the Rx-to-OTC switch. These data have been reviewed previously and determined to be adequate (Section 3.3: Choudary, 2000; Robison, 2000). The Sponsor is relying for nonclinical support on the Agency's previous findings of safety under NDA 021229.

This 505(b)(2) proposes a novel DR ODT formulation of omeprazole for use in adults 18 years of age and older in the OTC treatment of frequent heartburn with a recommended dosing regimen of 20 mg (1 tablet) per day for 14 days. The proposed formulation contains no novel excipients and only one excipient—ascorbic acid—has a proposed use level that slightly exceeds FDA IID-reported in-product use levels for ODT dosage forms. The Sponsor's submitted risk assessment in support of the [redacted] (b) (4) of the resulting increase in daily patient exposure to ascorbic acid ([redacted] (b) (4) mg/day to [redacted] (b) (4) mg/day) is considered adequate. All proposed DP impurity specifications have been adequately addressed with appropriate justification.

In conclusion, no original nonclinical data were included with the current NDA submission and none are required. Based on the totality of the information described above, NDA 209400 is deemed to be approvable from a nonclinical perspective.

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/s/

DONALD C THOMPSON
05/08/2017

JANE J SOHN
05/08/2017
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 209400 **Applicant: Dexcel Pharma Technologies, Ltd.** **Stamp Date: 6 Sep 2016**

Drug Name: Omeprazole DR ODT **NDA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			N/A
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		Clinical PK/BE study

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

DONALD C THOMPSON
10/26/2016

JANE J SOHN
11/02/2016
I concur.