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RESEARCH**

APPLICATION NUMBER:

209400Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA number:	209-400
Letter Date(s):	September 06, 2016
Brand Name (Proposed):	N/A
Generic Name:	Omeprazole
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Office of Nonprescription Products (ONP)
Sponsor:	Dexcel Pharma Technologies Ltd
Related IND(s):	127,169
Submission Type; Code	505 (b) (2)
Formulation; Strength(s)	Delayed-Release Orally Disintegrating Tablet; 20 mg
Pharmacological Class	Proton Pump Inhibitor
Indication	Treatment of frequent heartburns occurring 2 or more days a week, Over-the-counter (OTC)
Proposed dosing regimen	One tablet per day for a 14-day course of treatment
Listed Drug	Prilosec, OTC™ (Omeprazole Magnesium Delayed-Release Tablet, 20 mg Omeprazole)
Primary Reviewer :	Jie Cheng, Ph.D.
Secondary Reviewer :	Insook Kim, Ph.D.

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1. Executive Summary

In this submission, the applicant proposed a new delayed-release orally disintegrating tablet (ODT) formulation for 20 mg omeprazole for over-the-counter (OTC) use for the treatment of frequent heartburns occurring 2 or more days a week in adults. The proposed dosing regimen is one tablet per day for a 14-day course of treatment. For the efficacy and safety of the proposed ODT formulation, the sponsor proposed to rely on the efficacy and safety of the approved Prilosec, OTC (NDA 21-229; omeprazole magnesium delayed-release tablet, 20 mg of omeprazole; approved on June 20th, 2003). To support the reliance on Prilosec OTC, the sponsor provided the results of two relative bioavailability/bioequivalence studies, i.e., a study between the proposed omeprazole ODT and the omeprazole delayed-release tablet for OTC use, (NDA 22-032; omeprazole DR) and a study between omeprazole DR and Prilosec OTC. Omeprazole DR for OTC use was approved on December 04th, 2007 based on a bioequivalence with Prilosec OTC by the same applicant. The proposed indication for the proposed omeprazole ODT, 20 mg, OTC is the same as that approved for Prilosec OTC. The proposed dosing method is to disintegrate the ODT on the tongue and swallow with water or without water. In addition, swallowing whole tablet is also proposed.

In addition to the relative bioavailability study results, the food effect study results for omeprazole ODT and the results of the comparative dissolution and alcohol-induced dose-dumping in vitro studies were submitted. For the review of the comparative dissolution and alcohol-induced dose-dumping studies, please refer to the biopharmaceutics review.

The relative BA/BE study between omeprazole DR, 20 mg, OTC and Prilosec, 20 mg, OTC and the inspection of clinical and bioanalytical study sites was previously found acceptable to support the approval of NDA 22-032. Please refer to the clinical pharmacology review of the original submission of NDA 22-032 for more details.

1.1 Recommendation(s):

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 reviewed the application and found it acceptable for approval from a clinical pharmacology standpoint. The proposed new formulation was bridged to Prilosec 20 mg via two relative BA/BE studies that demonstrated bioequivalence between the proposed omeprazole ODT, 20 mg, OTC and the approved omeprazole DR, 20 mg, OTC and bioequivalence between the omeprazole DR, 20 mg, OTC and Prilosec, 20 mg, OTC Tablets (Listed drug).

The Office of Study Integrity and Surveillance (OSIS) recommended accepting the data from the relative BA/BE study between omeprazole ODT and omeprazole DR based on the acceptable findings from the inspection of the clinical and bioanalytical study sites. The OSIS report dated March 9th, 2017 stated that “No significant deficiencies were observed and no Form FDA 483 was issued at the close of the inspection. Based on the inspection findings, we recommend accepting data from all studies conducted at ^{(b) (4)} in pending ANDAs/NDAs for further Agency (FDA) review.”

1.2 Labeling Recommendations:

The proposed language of dosing method “Place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water.” is acceptable. The systemic exposure (C_{max} and AUC) following administration of omeprazole ODT swallowed with or without water or ODT swallowed whole with water was not significantly different amongst the dosing methods and from that of Omeprazole DR. In PK studies, the ODT disintegrated on tongue without water.

The proposed dosing method of “take 1 tablet before eating” is acceptable as high fat meal delayed the T_{max} and decreased the systemic exposure to omeprazole.

In addition, the proposed label of “Do not take this medicine with alcohol” is acceptable. Please refer to the biopharmaceutics review regarding to the alcohol-induced dose dumping study.

1.3 Summary of Clinical Pharmacology Findings:

Bioequivalence was demonstrated between omeprazole ODT and omeprazole DR:

Omeprazole ODT 20 mg, OTC when swallowed with water after disintegrating on tongue is bioequivalent (90% CI for C_{max} and AUC were within the BE criteria of 80-125%) to omeprazole DR, 20 mg, OTC which was swallowed whole with water in healthy subjects under fasted state (study #150075).

Bioequivalence was demonstrated between omeprazole DR and Prilosec:

Previously, the bioequivalence was demonstrated between omeprazole DR, 20 mg, OTC to Prilosec, 20 mg, OTC, Tablets (Listed drug) (Study AA24171 in NDA 22-032). Refer to the clinical pharmacology review of the original submission of NDA 22-032 for more details.

Bridging between omeprazole ODT and Prilosec

These two studies establish the bridge between the proposed omeprazole ODT 20 mg, OTC and Prilosec, OTC, 20 mg Tablets. Ideally a head-to-head comparison between omeprazole ODT and Prilosec should have been done. This indirect approach for bridging was discussed and agreed before NDA submission. In this cross-study comparison, the percent geometric mean ratios of C_{max} and AUC of omeprazole ODT vs. omeprazole DR and C_{max} and AUC of omeprazole DR vs. Prilosec were within +/- 5% from 100% and the 90% CI for both comparisons contained 100%. Therefore the bridging between omeprazole ODT and Prilosec OTC is acceptable without additional clinical trials for safety and efficacy.

Table 1 Bioequivalence assessment for PK parameters of omeprazole ODT vs. omeprazole DR and omeprazole DR vs. Prilosec (Listed drug)

	Point estimate (% Ratio between test vs. reference) (90% Confidence Interval)	
	Study 150075* (n=48)	Study AA24171 in NDA 22-032 ² (n=76)
PK Parameter	Omeprazole ODT ¹ vs. Omeprazole DR	Omeprazole DR vs. Prilosec
AUC _{0-t}	97.85% (92.64-103.34)	102.9% (99.0%-107.0%)
AUC _{inf}	96.89 (91.90-102.16)	104.2% (100.3%-108.3%)
C_{max}	99.99 (89.90-111.21)	99.8% (93.0%-107.1%)

¹Omeprazole ODT was allowed to disintegrate on tongue and swallowed without water

²See the clinical pharmacology review of the original submission of NDA 22-032

*Analysis by the reviewer, the conclusion is consistent with the sponsor’s analysis.

In addition, bioequivalence was demonstrated between omeprazole ODT administered by different administration methods, i.e., allowed to disintegrate on the tongue then swallowed with water or swallowed whole with water between omeprazole DR swallowed whole with water. As such after disintegration on tongue, ODT can be swallowed with or without water. The C_{max} and AUC between

omeprazole swallowed whole and omeprazole DR also met the bioequivalence criteria and supported the proposed dosing of ODT swallowed whole (Table 4).

Food Effect: The results of study #150076 indicated that administration of omeprazole ODT with a high-fat meal decreased mean C_{max} and AUC_{inf} by 56% and 19.2%, respectively, compared to those under fasted condition. In addition, T_{max} was delayed by approximately 2 hours in the fed state. The median (range) T_{max} values for the fed and fasted states were 4.5 h (2.0-16.0 h) and 2.17 h (1.0-4.50 h), respectively.

2. QBR

2.1 General Mechanism of Action

Omeprazole is 5-methoxy-2- [[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. The molecular formula is: $C_{17}H_{19}N_3O_3S$ and the molecular weight is: 345.42. Omeprazole is a proton pump inhibitor. It is believed to suppress gastric acid secretion by irreversible inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell.

2.2 Drug Composition

Omeprazole ODTs are round reddish mottled uncoated tablets. The unit composition (b) (4) is listed in the following table:

Table 2 Omeprazole ODT, 20mg, OTC final tablet composition

Ingredient	Weight per tablet (mg)	Function	Quality Standard
(b) (4)	(b) (4)	(b) (4)	--
(b) (4)	(b) (4)	(b) (4)	DMF holder standard
Microcrystalline Cellulose	(b) (4)	(b) (4)	NF
Crospovidone	(b) (4)	(b) (4)	NF
Sucralose	(b) (4)	(b) (4)	NF
Ascorbic Acid	(b) (4)	(b) (4)	USP
Strawberry flavor mixture	(b) (4)	(b) (4)	DMF holder standard
Colloidal Silicon Dioxide	(b) (4)	(b) (4)	NF
Sodium Stearyl Fumarate	(b) (4)	(b) (4)	NF
Ferric oxide	(b) (4)	(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

2.3 General Clinical Pharmacology

Q. What were the design features of the clinical pharmacology and/or pivotal clinical studies used to support efficacy and safety?

The applicant included three clinical pharmacology studies in this NDA. The design of the studies is reported in the table below:

Table 3 Summary of studies in current application

Study#	Type of Study and the Objective of the Study	Study Design
150075	A relative bioavailability study to assess the single-dose relative bioavailability of 20 mg omeprazole Delayed-	4-way crossover study in 48 healthy

	Release Orally Disintegrating tablets and omeprazole Delayed-Release tablets, OTC under fasting conditions.	subjects (32 males and 16 females)
150076	A food effect study to assess the effect of food on the bioavailability of 20 mg omeprazole Delayed-Release Orally Disintegrating tablets, OTC.	2-way crossover study in 18 healthy adults (10 males and 8 females)
AA24171	A previous reported relative bioavailability study to assess the single-dose relative bioavailability of 20 mg omeprazole Delayed-Release tablets, OTC and Prilosec, OTC, under fasting conditions.	2-way crossover study in 76 healthy subjects (42 males and 34 females)

No other clinical trials for safety or efficacy using the proposed omeprazole ODT were conducted.

Q. How the bridge between Prilosec and Omeprazole ODT was established?

The bridge was established indirectly based on the two BA/BE studies.

1) Relative bioavailability of Omeprazole ODT tablets compared to that of omeprazole DR tablets

The results of Study #150075 indicated that omeprazole ODT is bioequivalent to omeprazole DR tablet under fasting conditions. The 90% CI for the ratio of the geometric means of AUC_{0-t} , AUC_{inf} and C_{max} were within the bioequivalence acceptance criteria of 80-125% (Test 1 vs. Reference in Table 4). In addition, the bioavailability of omeprazole ODT was compared with that of omeprazole DR for difference dosing methods, i.e., disintegrated ODT swallowed without and with water and ODT swallowed whole without disintegrating on the tongue. The bioequivalence was demonstrated between ODT swallowed with water or ODT swallowed whole and Omeprazole DR swallowed whole with water. The reviewer's repeat analysis has confirmed these results.

Table 4 Relative bioavailability of omeprazole ODT tablets after administration by different methods compared to that of the omeprazole DR after administration as whole tablet

Dosing method for omeprazole ODT (Test)	PK Parameter	Test/Reference (% Ratio)	90% C.I.	
			Lower	Upper
Disintegrate on the tongue and <u>swallowed without</u> water	C_{max}	99.99	89.90	111.21
	AUC_{0-t}	97.85	92.64	103.34
	AUC_{0-inf}	96.89	91.90	102.16
Disintegrate on the tongue and <u>swallowed with</u> water	C_{max}	99.86	89.79	111.07
	AUC_{0-t}	95.96	90.86	101.35
	AUC_{0-inf}	95.13	90.23	100.30
Swallowed <u>whole with</u> water	C_{max}	103.21	92.76	114.83
	AUC_{0-t}	97.70	92.49	103.20
	AUC_{0-inf}	96.03	91.04	101.30

*Analysis by the reviewer. There were slight deviation of values between sponsor's analysis and reviewer's analysis. However, overall conclusion is consistent between analysis by the sponsor and the reviewer. See individual study review in page 11 for more details.

2) Relative bioavailability of Omeprazole ODT, Omeprazole DR tablets compared to that of Prilosec under fasting condition (Refer to clinical pharmacology review of the original submission

of NDA 22-032)

Table 5 Comparison of PK results of omeprazole ODT vs. omeprazole DR and omeprazole DR vs. Prilosec

Parameter	Study 150075		Omeprazole ODT vs. Omeprazole DR	Study AA24171		Omeprazole DR vs. Prilosec (Listed drug)
	Omeprazole ODT*	Omeprazole DR		Omeprazole DR	Prilosec	
C _{max} (ng/mL)	392.6±242.4	371.2±194.9	96.87% (87%-107.87%)	311.4±70.0	312.0±74.3	99.8% (93.0%-107.1%)
T _{max} (h)	2.3±0.8	2.3±0.9	--	2.4±45.3	2.2±44.2	--
AUC _{0-t} (ng·h/mL)	704.9±511.9	705.4± 519.7	99.06% (93.83%-104.58%)	440.3±93.6	428.0±99.8	102.9% (99.0%-107.0%)
AUC _{inf} (ng·h/mL)	709.7±513.9	717.9±526.5	98.96% (93.82%-104.39%)	448.9±94.5	438.4±100.6	104.2% (100.3%-108.3%)

* ODT disintegrated on the tongue and swallowed without water

Q. What are the Pharmacokinetic characteristics of Omeprazole ODT?

The single dose pharmacokinetics of omeprazole ODT was obtained from a single center, randomized, open-label, 4-way crossover study under fasting condition. The administration methods were omeprazole ODT placed on the tongue and administered without (Test 1, approximately 4±2 minutes for tablets to be disintegrated) or with water (Test 2), or given as a tablet with water (Test 3), versus omeprazole delayed-release tablet (Reference). Repeat analysis has confirmed this result. Although the PK values are slightly different between repeat analysis and the sponsor's analysis due to the slight difference of modeling settings for PK analysis, the difference in values doesn't change the conclusion of bioequivalence. The pharmacokinetic data and plotting curve are listed in the following table and figure (analysis by the reviewer):

Table 6 Descriptive Summary of the PK parameters of omeprazole ODT in Study# 150075

	Test 1 ¹				Test 2 ²			
	N	Mean	SD	CV%	N	Mean	SD	CV%
C _{max} (ng/mL)	48	392.6	242.44	61.75	48	386.93	226.68	58.58
T _{max} (h)	48	2.33	0.78	30.61	48	2.33	0.76	30.80
AUC _{inf} (ng·h/mL)	48	709.72	513.99	72.42	48	695.02	513.55	73.89
AUC _{last} (ng·h/mL)	48	704.92	511.87	72.61	48	689.51	510.88	74.09
T _{1/2} (h)	48	0.76	0.28	37.20	48	0.77	0.28	36.80
	Test 3 ³				Reference ⁴			
	N	Mean	SD	CV%	N	Mean	SD	CV%
C _{max} (ng/mL)	47	387.90	199.86	51.52	47	371.24	194.91	52.50
T _{max} (h)	47	2.33	1.35	55.80	47	2.33	0.92	36.47
AUC _{inf} (ng·h/mL)	46	660.91	466.96	70.65	46	717.92	526.51	73.34
AUC _{last} (ng·h/mL)	47	678.70	486.70	71.71	47	705.38	519.67	73.67
T _{1/2} (h)	46	0.83	0.35	41.50	46	0.78	0.31	40.02

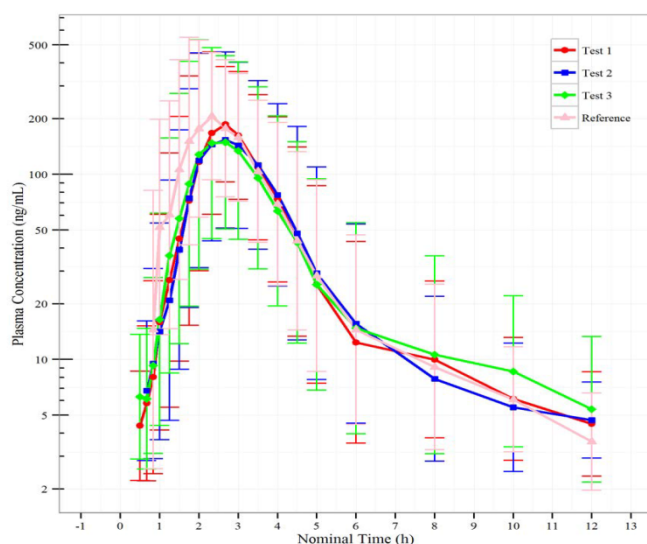
¹Test 1: Omeprazole ODT allowed to disintegrate on the tongue and swallowed without water.

²Test 2: Omeprazole ODT allowed to disintegrate on the tongue and swallowed with water.

³Test 3: Omeprazole ODT swallowed whole with water.

⁴Reference: Omeprazole DR swallowed whole with water.

Figure 1. Mean (SD) Omeprazole Plasma Concentration-Time Profile (Semi-log)



Test 1: Omeprazole ODT allowed to disintegrate on the tongue and swallowed without water.

Test 2: Omeprazole ODT allowed to disintegrate on the tongue and swallowed with water.

Test 3: Omeprazole ODT swallowed whole with water.

Reference: Omeprazole DR swallowed whole with water.

From the above table and figure, the results indicated that the pharmacokinetic parameters and plotting curve were very similar across omeprazole ODT with different administration methods. For example, the systemic exposure (C_{max} and AUC) following administration of ODT with or without water were not significantly different. ODT tablet can be administered with or without water. The similarity was also observed that PK parameters (C_{max} and AUC) after swallowing the whole ODT tablet were not significantly different from that after administration Omeprazole DR. The statistical analysis of AUC and C_{max} between omeprazole ODT in different administration methods and omeprazole DR is listed in the following table:

Table 7 Relative bioavailability of Omeprazole ODT tablets in Study #150075*

Parameter	Treatment Comparisons	Ratio	90% C.I.	
			Lower	Upper
AUC _{0-t}	Test 1 ¹ (A) – Test 2 ² (B)	101.96	97.50	106.63
	Test 1 (A) – Reference ⁴ (D)	97.85	92.64	103.34
	Test 2 (B) – Reference (D)	95.96	90.86	101.35
	Test 3 ³ (C) – Reference (D)	97.70	92.49	103.20
AUC _{0-inf}	Test 1 (A) – Test 2 (B)	101.85	97.43	106.47
	Test 1 (A) – Reference (D)	96.89	91.90	102.16
	Test 2 (B) – Reference (D)	95.13	90.23	100.30
	Test 3 (C) – Reference (D)	96.03	91.04	101.30
C _{max}	Test 1 (A) – Test 2 (B)	100.13	91.37	109.73
	Test 1 (A) – Reference (D)	99.99	89.90	111.21
	Test 2 (B) – Reference (D)	99.86	89.79	111.07
	Test 3 (C) – Reference (D)	103.21	92.76	114.83

¹ Test 1: Omeprazole ODT allowed to disintegrate on the tongue and swallowed without water.

² Test 2: Omeprazole ODT allowed to disintegrate on the tongue and swallowed with water.

³ Test 3: Omeprazole ODT swallowed whole with water.

⁴ Reference: Omeprazole DR swallowed whole with water.

*Analysis by the reviewer.

Q. What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

Food significantly affects the bioavailability of Omeprazole ODT. Repeat analysis has confirmed this result. The results of the food effect study (#150076) indicated that the rate and extent of absorption were decreased. The AUC_{0-t} and AUC_{inf} were decreased by approximately 21.8% and 19.2%, respectively, under fed conditions. There was also a decrease (56%) in C_{max} observed (see the following table).

Table 8 Food effect on omeprazole ODT bioavailability in Study #150076*

Pharmacokinetic Parameter	Fed (A)	Fasting (B)	Fed (A) vs. Fasting (B) Geometric Mean Ratio (90% CI)
C _{max} (ng/mL)	230.28±174.22	456.86±338.52	44.02% (32.40%-59.82%)
T _{max} (h)	4.50±3.66	2.17±0.88	--
AUC _{0-t} (ng·h/mL)	836.73±1238.76	1108.81±1459.17	78.20% (69.11%-88.48%)
AUC _{inf} (ng·h/mL)	904.36±1264.60	1072.18±1370.91	80.20% (70.02%-91.86%)

*Analysis by the reviewer.

In addition, T_{max} was found to be delayed by approximately 2 hours in the fed state. The median (range) T_{max} values for the fed and fasted states were 4.5 h (2.0-16.0 h) and 2.17 h (1.0-4.50 h), respectively. Therefore the applicant proposed labeling the product to be taken before meals in the morning. The Prilosec labeling claims to take Prilosec at least 1 hour before a meal, and the omeprazole DR labeling claims to “Swallow 1 tablet with a glass of water before eating in the morning.” Therefore, this proposed labeling language “Take tablet before eating in the morning” is consistent with those in the labeling of Prilosec and omeprazole DR.

2.4 Analytical

Q. Were the analytical methods used for the determination of omeprazole in biological fluids adequately validated?

All the samples were analyzed within the validated stability period (51 days). The validated bioanalytical method is listed as follows:

Method HPLC with Mass Spectrometric Detection	HPLC-MS/MS
Compound	Omeprazole
Internal Standard	(b) (4)
Matrix	Human EDTA K ₂ Plasma
Accuracy (%) and Precision (%) <i>Within-Day</i> <i>Between-Day</i>	Within-Day: Biases: -1.51 to 4.75% CV: 0.99 to 5.29% Between-Day: Biases: 0.08 to 7.28% CV: 1.29 to 5.67%
Standard curve range	2.00 to 1000.00 ng/mL
Dilution Integrity	Bias: -4.67%, CV: 3.74%
Sensitivity (LOQ)	Signal to noise ratio at 2.00 ng/mL
Selectivity	No significant interference observed in 6 out of 6 tested matrices for omeprazole and its IS
Recovery	Analyte: Means: 58.75, 57.51 and 57.69%, CV 1.16%

	IS: Mean: 59.42%
Carryover of Analyte and IS	No significant carryover observed
Potentially interfering and commonly used drugs	No effect on the quantitation of the analyte
Stability	< 2% degradation was observed following long term storage @-20°C in solution for 59 days; Short-term stability (low and high concentration) in solution ambient temperature for 45h42min and 23h26min; Short-term and long term stability in Matrix: 29h11min and 51 days; Stability of Analyte in Whole Blood: 180 minutes in an ice/water bath; 4 freeze-thaw cycles (-20°C and -80°C);
Conclusion	Method validation is acceptable.

The analytical method used in the study of AA24171 (for approval of NDA 22-032, omeprazole DR) analyzed the blood samples using HPLC-MS. The calibration range was 2.01 to 2010 ng/mL. The accuracy, precision, selectivity, sensitivity and stability etc. of the bioanalytical method validation fell into the FDA-accepted range, similar to the range of above bioanalytical method used in the current studies of #150075 and #150076. Please see the clinical pharmacology review of NDA 22-032 for more details.

3. Individual Study Review

1. Bioequivalence Study (Synopsis: Study # 150075)

Reviewer's comment: This study evaluated the bioequivalence of the proposed omeprazole delayed-release orally disintegrating tablet (omeprazole ODT), OTC with omeprazole delayed-release (omeprazole DR) tablet, OTC under fasting conditions.

Title: Randomized, open-label, 4-way crossover bioequivalence study of omeprazole delayed-release orally disintegrating tablet 20 mg and omeprazole delayed-release tablet (reference) following a 20 mg dose in healthy subjects under fasting conditions.

Objective: The objectives of this study were to compare the rate and extent of absorption of:

- Omeprazole Delayed-Release Orally Disintegrating Tablet 20 mg placed on the tongue and administered without (Test 1) or with water (Test 2) or given as a tablet with water (Test 3), versus Omeprazole Delayed-Release Tablet 20 mg (Reference), administered as 1×20 mg delayed-release orally dis-integrating tablet or delayed-release tablet under fasting conditions.
- Omeprazole Delayed-Release Orally Disintegrating Tablet 20 mg placed on the tongue and given without water (Test 1) versus with water (Test 2), administered as 1×20 mg delayed release orally disintegrating tablet under fasting conditions.

Study site (Clinical, Statistical, and Analytical):

(b) (4)

Study Dates:

First Subject First Visit: Nov 2nd, 2015

First Subject First Dose: Nov 30th, 2015

Last Subject Last visit: Dec, 28th, 2015

Study Design:

A single center, randomized, single-dose, open-label, 4-way crossover BE study to compare the rate and extent of absorption of Omeprazole Delayed-Release Orally Disintegrating Tablet placed on the tongue and administered without (Test 1) or with water (Test 2), or given as a tablet with water (Test 3), versus Omeprazole Delayed-Release Tablet (Reference), under fasting conditions. Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme. Subjects were confined 10 hours prior to drug administration until after the 12-hour post-dose blood draw, in each period. The treatment phases were separated by washout periods of seven days. Subjects were divided into four periods for dosing:

Treatment				
Treatment Identification:	Test (A)	Test (B)	Test (C)	Reference (D)
Product Name:	OMEPRAZOLE DR ORALLY DISINTEGRATING TABLETS 20 MG	OMEPRAZOLE DR ORALLY DISINTEGRATING TABLETS 20 MG	OMEPRAZOLE DR ORALLY DISINTEGRATING TABLETS 20 MG	OMEPRAZOLE DELAYED RELEASE TABLETS 20 MG
Company Responsible for Manufacturing:	Dexcel Pharma Technologies Ltd., Israel	Dexcel Pharma Technologies Ltd., Israel	Dexcel Pharma Technologies Ltd., Israel	Dexcel Pharma Technologies Ltd., Israel
Batch/Lot Number:	BY501014	BY501014	BY501014	Y1410059
Manufacturing Date:	Nov-2014	Nov-2014	Nov-2014	Nov-2014
Expiration Date:	(b) (4)			Nov-2016
Strength:	20 mg	20 mg	20 mg	20 mg
Dosage Form:	Delayed-release orally disintegrating tablet	Delayed-release orally disintegrating tablet	Delayed-release orally disintegrating tablet	Delayed release tablet
Dose Administered:	1 x 20 mg	1 x 20 mg	1 x 20 mg	1 x 20 mg
Potency:	99.4%	99.4%	99.4%	98.7% (19.7 mg/ tablet)
Route of Administration:	Oral	Oral	Oral	Oral

Pharmacokinetic blood sampling:

0 (pre-dose), 0.500, 0.667, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0, and 12.0 hour post-dose in each period.

Reviewer's comment: The sampling time for omeprazole is acceptable as the half-life of omeprazole is 0.5-1 hr.

Analytical Method: Omeprazole in plasma was analyzed using a validated LC/MS/MS method developed at (b) (4). The analytical range was 2 to 1000 ng/mL.

Pharmacokinetic and Statistical Analysis:

- Parametric ANOVA on AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , $T_{1/2}$, and K_{el} ; confidence intervals for AUC_{0-t} , AUC_{0-inf} , and C_{max} ;
- Factors in the ANOVA model: sequence, subject within sequence, period, and treatment;
- Ln-transformed parameters: AUC_{0-t} , AUC_{0-inf} , and C_{max} .

Standards for Bioequivalence:

Omeprazole Delayed-Release Orally Disintegrating Tablet vs Omeprazole Delayed-Release Tablet (A-Test 1, B-Test 2, C-Test 3, and D-Reference)

- The 90% confidence intervals of the ratio (A/D, B/D, and C/D) of least-squares means from the ANOVA of the ln-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} must be within 80.00% to 125.00%.

Effect of water on Omeprazole Delayed-Release Orally Disintegrating Tablet

- The 90% confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} must be within 80.00% to 125.00%.

Results:

1.1 Demographic data:

Table 9 Summary of Demographics and Body Measurements Data of Subjects

Category		Safety Population N=48
Age (years)	Mean ± SD	53 ± 12
	Range	23 - 71
	Median	54
Age Groups	<18	0
	18-40	6 (12.5%)
	41-64	33 (68.8%)
	65-75	9 (18.8%)
	>75	0
Gender	Male	32 (66.7%)
	Female	16 (33.3%)
Race	Asian	0
	Black/African American	0
	White	48 (100%)
	Other	0
Ethnicity	Not Hispanic	46 (95.8%)
	Hispanic	2 (4.2%)
BMI (kg/m ²)	Mean ± SD	25.48 ± 2.29
	Range	19.79 - 28.74
	Median	25.66
Height (cm)	Mean ± SD	169.6 ± 7.7
	Range	153.5 - 187.0
	Median	169.0
Weight (kg)	Mean ± SD	73.35 ± 8.45
	Range	56.20 - 90.20
	Median	73.90

N: Number of observations; SD: Standard deviation; BMI: Body Mass Index.

Other: Multi-racial, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander.

Reviewer Comments: Per protocol, Asians were excluded due to a potential inclusion of CYP2C19 poor metabolizers as CYP2C19 deficiency is more prevalent in Asians than in other races. CYP2C19 is the major enzyme that metabolizes omeprazole. In studies of single omeprazole doses, an approximate four-fold increase in AUC was noted in Asian subjects compared to Caucasians. It is acceptable to exclude subject of Asian origin to reduce the variability for this bioequivalence study although ideally genotyping should have been used for exclusion of CYP2C19 poor metabolizers.

1.2 Pharmacokinetic Results

Omeprazole concentration-time profiles are shown below.

Figure 2. Mean (SD) Omeprazole Plasma Concentration-Time Profile (Linear) after administration of 20 mg ODT (TEST 1,2, and 3) and DR (reference)

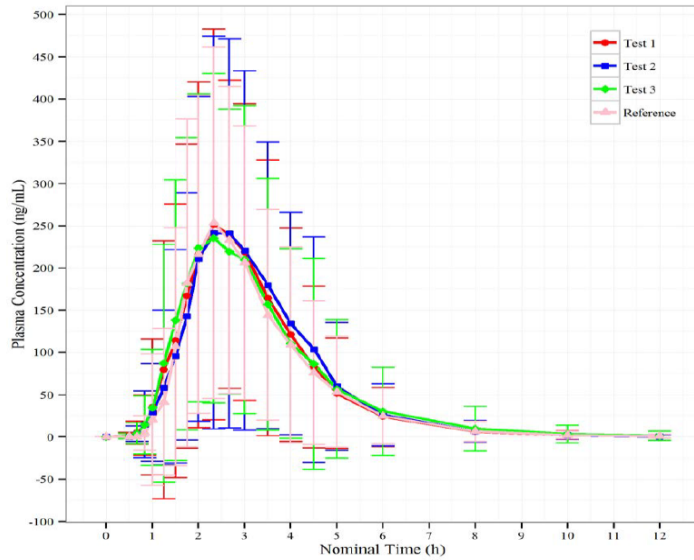
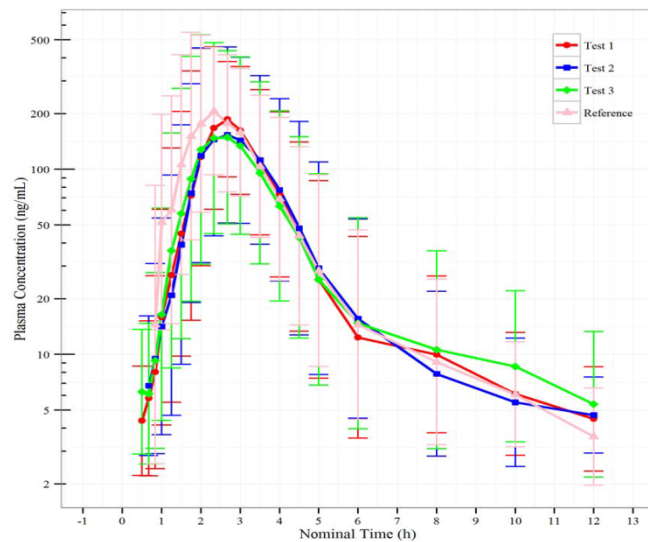


Figure 3. Mean (SD) Omeprazole Plasma Concentration-Time Profile (Semi-log)



Test 1: Omeprazole ODT allowed to disintegrate on the tongue and swallowed without water.

Test 2: Omeprazole ODT allowed to disintegrate on the tongue and swallowed with water.

Test 3: Omeprazole ODT swallowed whole with water.

Reference: Omeprazole DR swallowed whole with water.

Table 10 Descriptive Summary of the PK parameters of omeprazole

Parameter (units)	Omeprazole DR ODT (Test 1)				Omeprazole DR ODT (Test 2)			
	N	Mean	SD	CV%	N	Mean	SD	CV%
AUC ₀₋₄ (h*ng/mL)	48	689.51	510.88	74.09	48	704.92	511.87	72.61
AUC _{0-inf} (h*ng/mL)	48	694.96	513.54	73.89	48	709.70	514.01	72.43
Residual area (%)	48	0.96	0.53	55.71	48	0.85	0.48	56.40
C _{max} (ng/mL)	48	386.93	226.68	58.58	48	392.61	242.44	61.75
T _{½ el} (h)	48	0.76	0.28	36.29	48	0.76	0.28	36.64
K _{el} (/h)	48	1.0105	0.3086	30.5394	48	1.0234	0.3273	31.9829
Correlation	48	-0.9970	0.0034	-0.3427	48	-0.9965	0.0041	-0.4083
K _{el Lower} (h)	48	4.35	0.729	16.7	48	4.39	0.746	17.0
K _{el Upper} (h)	48	7.32	2.22	30.3	48	7.52	2.26	30.0

Parameter (units)	Omeprazole DR ODT (Test 3)				Omeprazole DR Tablet (Reference)			
	N	Mean	SD	CV%	N	Mean	SD	CV%
AUC ₀₋₄ (h*ng/mL)	47	705.38	519.67	73.67	46	655.37	464.75	70.91
AUC _{0-inf} (h*ng/mL)	47	712.32	522.18	73.31	46	661.06	467.01	70.65
Residual area (%)	47	1.12	1.23	110.33	46	1.07	0.79	73.46
C _{max} (ng/mL)	47	371.24	194.91	52.50	46	378.85	192.08	50.70
T _{½ el} (h)	47	0.78	0.30	38.67	46	0.85	0.35	41.28
K _{el} (/h)	47	0.9922	0.3077	31.0130	46	0.9349	0.3095	33.1107
Correlation	47	-0.9957	0.0108	-1.0881	46	-0.9953	0.0081	-0.8125
K _{el Lower} (h)	47	4.44	0.956	21.5	46	4.49	0.861	19.2
K _{el Upper} (h)	47	7.45	2.39	32.1	46	7.73	2.54	32.9

Table 11 Statistical analysis of Omeprazole-Ratios and Confidence Intervals.

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC ₀₋₄	Test 1 (A) - Test 2 (B)	98.07%	92.97%	103.45%	15.89%	68.28%
	Test 1 (A) - Reference (D)	99.06%	93.83%	104.58%		
	Test 2 (B) - Reference (D)	101.01%	95.68%	106.63%		
	Test 3 (C) - Reference (D)	103.28%	97.82%	109.05%		
AUC _{0-inf}	Test 1 (A) - Test 2 (B)	98.18%	93.15%	103.48%	15.64%	68.02%
	Test 1 (A) - Reference (D)	98.96%	93.82%	104.39%		
	Test 2 (B) - Reference (D)	100.80%	95.56%	106.33%		
	Test 3 (C) - Reference (D)	103.35%	97.96%	109.03%		
C _{max}	Test 1 (A) - Test 2 (B)	99.87%	89.84%	111.03%	32.10%	46.24%
	Test 1 (A) - Reference (D)	96.87%	87.00%	107.87%		
	Test 2 (B) - Reference (D)	97.00%	87.11%	108.01%		
	Test 3 (C) - Reference (D)	97.20%	87.26%	108.26%		

¹ Calculated using least-squares means according to the formula: e^(DIFFERENCE) X 100.

² 90% Geometric Confidence Interval using ln-transformed data.

Test 1 (A): Omeprazole ODT allowed to disintegrate on the tongue and swallowed without water.

Test 2 (B): Omeprazole ODT allowed to disintegrate on the tongue and swallowed with water.

Test 3 (C): Omeprazole ODT swallowed whole with water.

Reference (D): Omeprazole DR swallowed whole with water.

N=48 for comparison A/B, and N=46 for comparisons A/D, B/D, and C/D.

Table 12 Statistical analysis of T_{max} of omeprazole ODT and omeprazole DR using non-parametric analysis is shown below.

Parameter (units)	Omeprazole DR ODT (Test 1)				Omeprazole DR ODT (Test 2)			
	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	48	2.33	1.25	4.50	48	2.33	1.25	4.50
Parameter (units)	Omeprazole DR ODT (Test 3)				Omeprazole DR Tablet (Reference)			
	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	47	2.33	1.25	6.00	46	2.17	1.00	5.00

1.3 Conclusions:

- The omeprazole ODT without or with water or given as a tablet with water is bioequivalent with omeprazole DR tablet (90% CIs for the ratios of geometric AUC_{0-last} and AUC_{0-inf} were within the 0.80 to 1.25 range) or on C_{max} .

1.4 Repeat Analysis by this reviewer:

Table 13 Repeat analysis of Descriptive Summary of the PK parameters of omeprazole

	Test 1				Test 2			
	N	Mean	SD	CV%	N	Mean	SD	CV%
AUC_{inf}	48	709.72	513.99	72.42	48	695.02	513.55	73.89
AUC_{last}	48	704.92	511.87	72.61	48	689.51	510.88	74.09
C_{max}	48	392.6	242.44	61.75	48	386.93	226.68	58.58
$T_{1/2}$	48	0.76	0.28	37.20	48	0.77	0.28	36.80
K_{el}	48	1.02	0.34	33.10	48	1.00	0.32	31.58
	Test 3				Reference			
	N	Mean	SD	CV%	N	Mean	SD	CV%
AUC_{inf}	46	660.91	466.96	70.65	46	717.92	526.51	73.34
AUC_{last}	47	678.70	486.70	71.71	47	705.38	519.67	73.67
C_{max}	47	387.90	199.86	51.52	47	371.24	194.91	52.50
$T_{1/2}$	46	0.83	0.35	41.50	46	0.78	0.31	40.02
K_{el}	46	0.95	0.33	34.23	46	1.01	0.33	32.36

Table 14 Repeat analysis of Statistical analysis of Omeprazole-Ratios and Confidence Intervals

Parameter	Treatment Comparisons	Ratio	90% C.I.		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC_{0-t}	Test 1 (A) –Test 2 (B)	101.96	97.50	106.63	13.11%	72.19%
	Test 1 (A)–Reference (D)	97.85	92.64	103.34		
	Test 2 (B)–Reference (D)	95.96	90.86	101.35		
	Test 3 (C)–Reference (D)	97.70	92.49	103.20		
AUC_{0-inf}	Test 1 (A) –Test 2 (B)	101.85	97.43	106.47	13.00%	71.85%
	Test 1 (A)–Reference (D)	96.89	91.90	102.16		
	Test 2 (B)–Reference (D)	95.13	90.23	100.30		
	Test 3 (C)–Reference (D)	96.03	91.04	101.30		
C_{max}	Test 1 (A) –Test 2 (B)	100.13	91.37	109.73	27.18%	55.54%
	Test 1 (A)–Reference (D)	99.99	89.90	111.21		

	Test 2 (B)–Reference (D)	99.86	89.79	111.07		
	Test 3 (C)–Reference (D)	103.21	92.76	114.83		

Table 15 Repeat Analysis of Statistical analysis of T_{max} of omeprazole ODT and omeprazole DR

Parameter (units)	Omeprazole DR ODT (Test 1)				Omeprazole DR ODT (Test 2)			
	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	48	2.33	1.25	4.50	48	2.33	1.25	4.50
Parameter (units)	Omeprazole DR ODT (Test 3)				Omeprazole DR Tablet (Reference)			
	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	47	2.33	1.00	10.00	47	2.33	1.25	6.00

Reviewer's comment: The repeat analysis using Winnonlin Phoenix 64 confirmed the sponsor's results that the omeprazole ODT swallowed without or with water or swallowed as a whole tablet with water is bioequivalent with omeprazole DR tablet (90% CIs for the ratios of geometric AUC_{0-last} and AUC_{0-inf} were within the 0.80 to 1.25 range) or on C_{max} .

2. Food effect Study (Synopsis: Study # 150076)

Reviewer's comment: This study evaluated the food effect on omeprazole ODT under fed and fasting conditions.

Title: Randomized, open-label, 2-way crossover design, comparative bioavailability, food-effect study of omeprazole delayed-release orally disintegrating tablet 20 mg.

Objective: The objective of this study was to assess the effect of food on the pharmacokinetics (PKs) of Omeprazole Delayed-Release Orally Disintegrating Tablet 20 mg administered as 1 x 20 mg delayed-release orally disintegrating tablet under fasting and fed conditions.

Study site (Clinical, Statistical, and Analytical):

(b) (4)

Study Dates:

First Subject First Visit: Nov 2nd, 2015
 First Subject First Dose: Nov 30th, 2015
 Last Subject Last visit: Dec, 28th, 2015

Study Design:

This was a single center, randomized, single-dose, open-label, 2-way comparative BA study to assess the effect of food on the PKs of Omeprazole ODT formulation, under fasting and fed conditions. Subjects were confined from at least 11 hours prior to drug administration until after the 24.0-hour post-dose blood draw, in each period. The treatment phases were separated by a washout period of seven days.

Pharmacokinetic blood sampling:

For fed condition, blood samples were collected prior to drug administration and 0.500, 1.00, 1.50, 2.00,

2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 9.00, 10.0, 12.0, 14.0, 16.0, 20.0, and 24.0 hours post dose, in each period.

For fasting condition, blood samples were collected prior to drug administration and 0.500, 0.667, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0 and 12.0 hours post-dose, in each period.

Reviewer's comment: The sampling time for omeprazole is acceptable as the half-life of omeprazole is 0.5-1 hr.

Analytical Method: Omeprazole in plasma was analyzed using a validated LC/MS/MS method developed at (b) (4). The analytical range was 2 to 1000 ng/mL.

Pharmacokinetic and Statistical Analysis:

Pharmacokinetics:

- Parametric ANOVA on AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , $T_{1/2}$, and K_{el} ; confidence intervals for AUC_{0-t} , AUC_{0-inf} , and C_{max} ;
- Factors in the ANOVA model: sequence, subject within sequence, period, and treatment;
- Ln-transformed parameters: AUC_{0-t} , AUC_{0-inf} , and C_{max} .

Criteria for no food effect for omeprazole:

- 90% confidence intervals of the ratio (Fed/Fasting) of least-squares means from the ANOVA of the ln-transformed AUC_{0-t} , AUC_{0-inf} and C_{max} must be within 80.00% to 125.00%.

Results:

2.1 Demographic data:

Table 16 Summary of Demographics and Body Measurements Data of Subjects

Category		Safety Population N=18
Age (years)	Mean ± SD	48 ± 15
	Range	21 - 69
	Median	46
Age Groups	<18	0
	18-40	6 (33.3%)
	41-64	9 (50.0%)
	65-75	3 (16.7%)
	>75	0
Gender	Male	10 (55.6%)
	Female	8 (44.4%)
Race	Asian	0
	Black/African American	0
	White	18 (100%)
	Other	0
Ethnicity	Not Hispanic	18 (100%)
	Hispanic	0
BMI (kg/m ²)	Mean ± SD	26.23 ± 2.05
	Range	22.79 - 29.41
	Median	26.27
Height (cm)	Mean ± SD	167.3 ± 7.6
	Range	153.0 - 182.0
	Median	168.0
Weight (kg)	Mean ± SD	73.66 ± 9.38
	Range	55.80 - 87.20
	Median	75.20

2.2 Pharmacokinetic Results

Omeprazole concentration-time profiles are shown below.

Figure 4. Mean (SD) Omeprazole Plasma Concentration-Time Profile after administration of ODT under fasting (blue) and fed condition (red)(Linear)

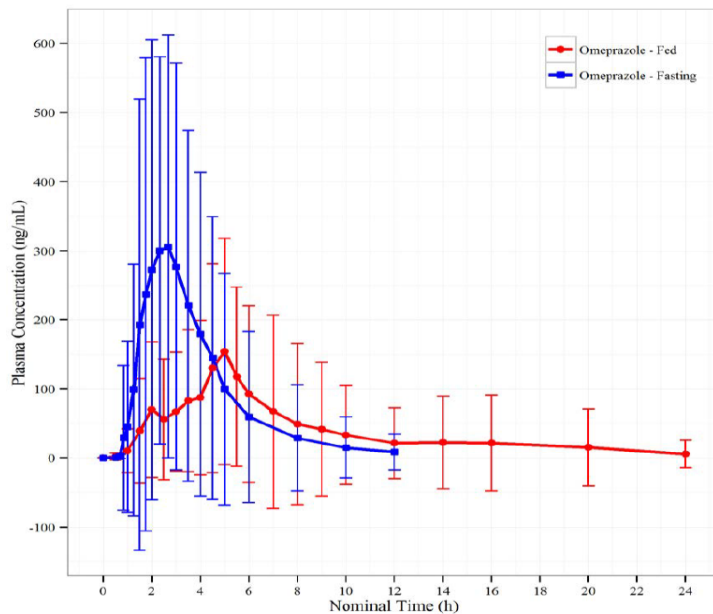


Figure 5. Mean (SD) Omeprazole Plasma Concentration-Time Profile (Semi-log)

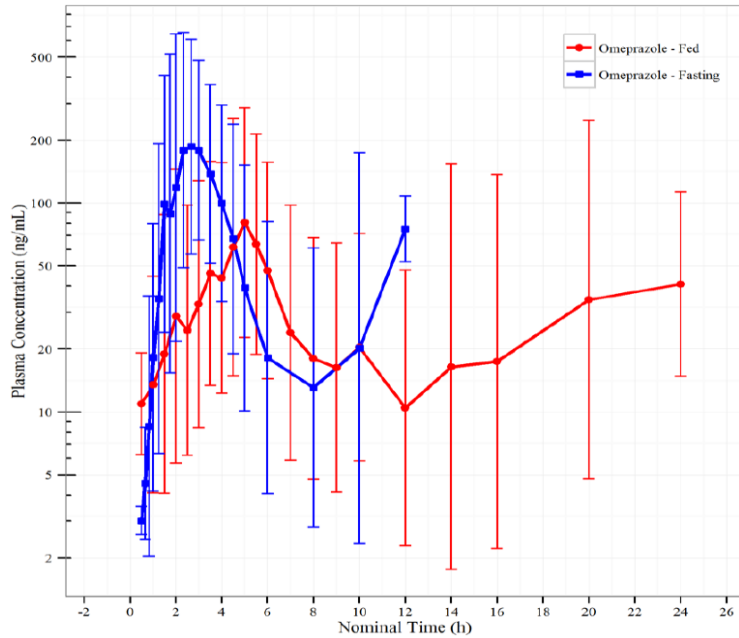


Table 17 Descriptive Summary of the PK parameters for Omeprazole under Fed and Fasting condition.

Parameter (units)	Omeprazole - Fed				Omeprazole - Fasting			
	N	Mean	SD	CV%	N	Mean	SD	CV%
AUC _{0-t} (h*ng/mL)	18	904.36	1264.60	139.83	18	1072.18	1370.91	127.86
AUC _{0-inf} (h*ng/mL)	15	1092.95	1430.02	130.84	15	1273.64	1553.50	121.97
Residual area (%)	15	2.83	3.85	135.92	15	1.57	1.86	118.46
C _{max} (ng/mL)	18	230.28	174.22	75.66	18	458.86	338.52	73.77
T _{½ el} (h)	15	1.66	1.14	68.50	15	1.01	0.65	63.84
K _{el} (/h)	15	0.5727	0.2789	48.6992	15	0.8534	0.3195	37.4372
Correlation	15	-0.9517	0.0622	-6.5376	15	-0.9964	0.0049	-0.4929
K _{el Lower} (h)	15	8.37	3.03	36.2	15	4.63	0.667	14.4
K _{el Upper} (h)	15	12.7	5.12	40.2	15	8.13	2.07	25.4

Table 18 Statistical analysis of the food effects

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC _{0-t}	Fed – Fasting	78.20%	69.11%	88.48%	21.48%	108.35%
AUC _{0-inf}	Fed – Fasting	80.20%	70.02%	91.86%	21.18%	106.61%
C _{max}	Fed – Fasting	44.02%	32.40%	59.82%	56.55%	60.86%

¹ Calculated using least-squares means according to the formula: $e^{(\text{DIFFERENCE})} \times 100$.

² 90% Geometric Confidence Interval using ln-transformed data.

Table 19 Statistical analysis of T_{max} from food effect study

Parameter (units)	Omeprazole - Fed				Omeprazole - Fasting			
	N	Median	Min	Max	N	Median	Min	Max
T _{max} (h)	18	4.50	2.00	16.0	18	2.17	1.00	4.50

2.3 Conclusion

The rate and extent of absorption are approximately 22% and 56% lower while the peak of absorption is delayed by approximately 2.33 hours when a 20 mg dose of omeprazole ODT is administered with food.

2.4 Repeat Analysis by this reviewer:

Table 20 Repeat analysis of Descriptive Summary of the PK parameters of omeprazole ODT-Fed/Fast

	Fed				Fast			
	N	Mean	SD	CV%	N	Mean	SD	CV%
AUC _{inf}	16.00	836.73	1238.76	148.05	18.00	1108.81	1459.17	131.60
AUC _{last}	18.00	904.36	1264.60	139.83	18.00	1072.18	1370.91	127.86
C _{max}	18.00	230.28	174.22	75.66	18.00	458.86	338.52	73.77
T _{1/2}	16.00	1.61	1.21	75.21	18.00	0.97	0.60	62.49
K _{el}	16.00	0.59	0.27	45.92	18.00	0.89	0.35	39.16

Table 21 Repeat analysis of Statistical analysis of Omeprazole-Ratios and Confidence Intervals

Parameter	Treatment Comparisons	Ratio	90% C.I.		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC _{0-t}	Fed (A) –Fast (B)	78.20	69.10	88.48	21.48%	108.35%
AUC _{0-inf}	Fed (A) –Fast (B)	80.75	70.94	91.92	20.88%	110.04%
C _{max}	Fed (A) –Fast (B)	44.02	32.40	59.81	56.55%	60.86%

Table 22 Repeat Analysis of Statistical analysis of T_{max} of omeprazole ODT Fed/Fast

Parameter (units)	Omeprazole DR ODT (Fed)				Omeprazole DR ODT (Fast)			
	N	Median	Min	Max	N	Median	Min	Max
T _{max} (h)	18	4.50	2.00	16.00	18	2.17	1.00	4.50

Conclusions:

Reviewer's comment: The repeat analysis using Winnonlin Phoenix 64 confirmed the sponsor's results that approximately 22% and 56% lower for AUC_{0-t} and C_{max} while the T_{max} is delayed by approximately 2.33 hours when a 20 mg dose of omeprazole ODT is administered with food.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIE CHENG
05/26/2017

INSOOK KIM
05/26/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	209400	SDN	1
Applicant	Dexcel Pharma Technologies Ltd	Submission Date	09/06/2016
Generic Name	Omeprazole	Brand Name	
Drug Class	Proton Pump Inhibitors (PPI)		
Indication	Treatment of Frequent Heartburn (over-the-counter)		
Dosage Regimen	1 tablet daily before eating in the morning, for 14 days		
Dosage Form	20 mg Delayed Release (DR), Orally Disintegrating Tablets (ODT)	Route of Administration	Oral
OCP Division	DCP III	OND Division	DNDP/DGIEP
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Sandhya Apparaju, Ph.D.	Sue Chih Lee, Ph.D.	
Pharmacometrics	N/A	N/A	
Genomics	N/A	N/A	
Review Classification	☒ Standard ☐ Priority ☐ Expedited		
Filing Date	11/5/2016	74-Day Letter Date	11/19/2016
Review Due Date	5/17/2017	PDUFA Goal Date	7/7/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

Yes

No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

Yes

No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

Yes

No

[Clinical trial 150075 will need inspection as it provides pivotal support to approval; Trial AA24171 was previously inspected and found acceptable by OCP in June 2007]

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☒ Yes ☐ No	Clinical Pharmacology Summary	☒ Yes ☐ No
Bioanalytical and Analytical Methods	☒ Yes ☐ No	Labeling	☒ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		

☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☒ Relative Bioavailability		Studies 150075 [relative BA/BE] and 150076 [food effect on PK] will be reviewed; Study AA24171 [relative BA/BE] was reviewed under NDA 22032 and found acceptable. It will not be reviewed again, but study findings will be considered during NDA decisions.
☒ Bioequivalence		See above
☒ Food Effect		
☒ Other		In vitro alcohol dose dumping study [for ONDQA/biopharm team review]
Human Pharmacokinetics		
Healthy Subjects	☐ Single Dose	
	☐ Multiple Dose	
Patients	☐ Single Dose	
	☐ Multiple Dose	
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		

☐ Exposure-Safety			
Total Number of Studies	In Vitro		In Vivo 3
Total Number of Studies to be Reviewed			2

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☒ Yes ☐ No ☐ N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐ Yes ☐ No ☒ N/A	505b(2) NDA relies upon reference drug(s).
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☒ Yes ☐ No ☐ N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☒ Yes ☐ No ☐ N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☒ Yes ☐ No ☐ N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐ Yes ☐ No ☒ N/A	505b(2) NDA relies upon reference drug(s).
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☒ Yes ☐ No ☐ N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☒ Yes ☐ No ☐ N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☒ Yes ☐ No ☐ N/A	
Complete Application		
10. Did the applicant submit studies including study reports, analysis datasets, source code, input	☒ Yes ☐ No ☐ N/A	

files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☒ Yes ☐ No ☐ N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐ Yes ☐ No ☒ N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☒ Yes ☐ No ☐ N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐ Yes ☐ No ☒ N/A	505b(2) NDA relies upon reference drug(s).
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐ Yes ☐ No ☒ N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐ Yes ☐ No ☒ N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐ Yes ☐ No ☒ N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☒ Yes ☐ No ☐ N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐ Yes ☐ No ☒ N/A	

Filing Memo

Omeprazole 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. Omeprazole works by inactivating the final step of the gastric acid secretion pathway in gastric parietal cells. This leads to inhibition of both basal and stimulated gastric acid secretion.

Dexcel Pharma Technologies (herein referred to as DPT or the Sponsor) submits this new drug application (NDA) for over the counter (OTC) Omeprazole Delayed-Release orally disintegrating tablet (ODT), utilizing the 505(b) (2) regulatory pathway. The proposed indication is the treatment of frequent heartburn.

The Sponsor intends to rely upon the Agency's prior findings of safety and efficacy for the reference listed drug (LD), Prilosec OTC (omeprazole; AstraZeneca NDA 021229), in conjunction with information from the public domain, to support the approval of this application. The Pre-IND meeting was held on October 6, 2015 and the Pre-NDA was held on May 9, 2016.

DPT has submitted results from comparative bioequivalence studies [Study 150075 and Study AA24171 (conducted for the approval of Omeprazole DR, NDA 022032)] and a bioavailability-food effect study (Study 150076) to provide the scientific "bridge" to the Agency's finding of safety and efficacy for Prilosec OTC.

Trial ID	Test / Batch #/ Sponsor	Ref Trt; Formulation /NDA #/Batch # /Sponsor	Clinical and Bioanalytical facilities
Study 150075	Omeprazole DR, ODT 20 mg Tablet taken without water (test 1), with water (test 2), or swallowed intact with water (test 3); Batch No.: BY501014 Dexcel Pharma Technologies Ltd, Israel	Omeprazole DR Tablet NDA # 22032 Batch No.: Y1410059 Dexcel Pharma Technologies Ltd, Israel	(b) (4)
Study AA24171	Omeprazole DR tablets 20 mg OTC (test); Conducted under NDA 22032 Batch No.: B0415 Dexcel Pharma Technologies Ltd, Israel Report Date: Oct 19, 2005	Prilosec DR tablets OTC NDA 21229 Lot No.: 43441711971 Astrazeneca	Clinical Site: Bioanalytical site:

			(b) (4)
Study 150076	Omeprazole 20 mg DR ODT tablet; fed (test; typical ODT use with no water) Batch No.: BY501014 Dexcel Pharma Technologies Ltd	Omeprazole 20 mg DR ODT tablet; fasted (reference; typical ODT use with no water) Batch No.: BY501014 Dexcel Pharma Technologies Ltd	(b) (4) Denis Audet, M.D. (P.I.)

DPT did not conduct any nonclinical or clinical studies in support of this application. Rather, the pharmacokinetic studies conducted aimed at establishing a scientific bridge between DPT's Omeprazole Delayed-Release orally disintegrating tablet and the LD, Prilosec OTC.

Waiver of In Vivo Alcohol-Induced Dose Dumping Testing: As discussed during the pre-NDA meeting 9 May 2016, DPT conducted an in vitro alcohol dose dumping study, demonstrating premature release of omeprazole with alcohol at concentrations of ~ 40%. In order to reduce the possibility of loss of efficacy due to co-administration with alcohol, a clear instruction not to take this medicine with alcohol is included in the proposed labeling. DPT is requesting a waiver of the in vivo alcohol dose dumping study for this NDA.

Sponsor notes that "Since the proposed Omeprazole ODT was determined to be bioequivalent to Omeprazole DR (NDA 022032), regardless of dosing condition (with and without water), DPT has included the proposed direction (label): "Take 1 tablet before eating in the morning. Place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water."

The Sponsor will be relying on the following information that the Sponsor does not own or have a right of reference to:

Source	Information Provided
Two clinical studies conducted for the approval of Prilosec OTC (Allgood, 2005)	Clinical efficacy of omeprazole 20 mg in the treatment of frequent heartburn
Two clinical studies conducted for the approval of Prilosec OTC (Allgood, 2005)	Clinical Safety of omeprazole 20 mg in the treatment of frequent heartburn

Published literature (2011- 2016) FAERS database (Q1 2008-Q4 2015) NPDS (2008-September 2015) WHO drug alert, newsletters 2008-2016) DAWN (2008-2011) ²	Clinical safety
FDA determination for Prilosec OTC (NDA 021229) ¹ labeling Summary of drug-drug interaction in the review of NDA 021229 WHO drug alert, newsletters 2008-2016	Pharmacokinetic Drug Interactions
FDA determination for Prilosec OTC (NDA 021229) ¹ , literature	Nonclinical safety of omeprazole, including reproductive toxicity studies
The Inactive Ingredient Database (IID), Safety report (based on literature and IID) for Ascorbic acid	Nonclinical safety of excipients
FDA determination for Prilosec OTC (NDA 021229) ¹	Pharmacodynamics and Mechanism of Action
FDA determination for Prilosec OTC (NDA 021229) ¹	Pharmacokinetics- ADME
FDA determination for Prilosec OTC (NDA 021229) ¹	Pharmacokinetics: Special Populations

¹ AstraZeneca does not appear to have conducted PK studies to assess drug interactions, PD studies, or non-clinical studies for Prilosec OTC, instead they provided a cross reference to Prilosec Rx (019810).

² The DAWN database was discontinued on 2011.

Results from the PK studies (pending review):

Study 150075: Ratios (A/B, A/D, B/D and C/D) and 90% geometric confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} for omeprazole [Reference treatment is Dexcel's omeprazole DR tablet 20 mg; NDA 22032]

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC _{0-t}	Test 1 (A) - Test 2 (B)	98.07%	92.97%	103.45%	15.89%	68.28%
	Test 1 (A) - Reference (D)	99.06%	93.83%	104.58%		
	Test 2 (B) - Reference (D)	101.01%	95.68%	106.63%		
	Test 3 (C) - Reference (D)	103.28%	97.82%	109.05%		
AUC _{0-inf}	Test 1 (A) - Test 2 (B)	98.18%	93.15%	103.48%	15.64%	68.02%
	Test 1 (A) - Reference (D)	98.96%	93.82%	104.39%		
	Test 2 (B) - Reference (D)	100.80%	95.56%	106.33%		
	Test 3 (C) - Reference (D)	103.35%	97.96%	109.03%		
C _{max}	Test 1 (A) - Test 2 (B)	99.87%	89.84%	111.03%	32.10%	46.24%
	Test 1 (A) - Reference (D)	96.87%	87.00%	107.87%		
	Test 2 (B) - Reference (D)	97.00%	87.11%	108.01%		
	Test 3 (C) - Reference (D)	97.20%	87.26%	108.26%		

¹ Calculated using least-squares means according to the formula: $e^{(\text{DIFFERENCE})} \times 100$.

² 90% Geometric Confidence Interval using ln-transformed data.

Test 1= Dexcel Pharma Technologies Ltd., Israel, Omeprazole 1 x 20 mg delayed-release orally disintegrating tablet allowed to disintegrate on the tongue and swallowed without water.

Test 2= Dexcel Pharma Technologies Ltd., Israel, Omeprazole 1 x 20 mg delayed-release orally disintegrating tablet allowed to disintegrate on the tongue and swallowed with water.

Test 3= Dexcel Pharma Technologies Ltd., Israel, Omeprazole 1 x 20 mg delayed-release orally disintegrating tablet swallowed whole with water.

Reference= Dexcel Pharma Technologies Ltd., Israel, Omeprazole 1 x 20 mg delayed-release tablet swallowed with water.

Study AA24171(reviewed and accepted under NDA 22302): Comparing Dexcel's omeprazole 20 mg DR OTC tablet vs. reference Prilosec DR OTC

Summary of Pharmacokinetic Results for Omeprazole

Parameter	Dexcel Ltd. (A) vs. P& G AstraZeneca (B)
AUC 0-t	102.9% (99.0% – 107.0%)
AUCinf	104.2% (100.3% – 108.3%)
Cmax	99.8% (93.0% – 107.1%)

Study 150076: Ratios and 90% geometric confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} for omeprazole

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC _{0-t}	Fed - Fasting	78.20%	69.11%	88.48%	21.48%	108.35%
AUC _{0-inf}	Fed – Fasting	80.20%	70.02%	91.86%	21.18%	106.61%
C _{max}	Fed – Fasting	44.02%	32.40%	59.82%	56.55%	60.86%

¹ Calculated using least-squares means according to the formula: $e^{(\text{Difference})} \times 100$.

² 90% Geometric Confidence Interval using ln-transformed data.

Datasets and bioanalytical methods: Electronic datasets, bioanalytical reports, method validation reports could be located for clinical trials 150075 and 150076. The same couldn't be located for study AA24171. In addition, the study report for AA24171 is described as 'partial' study report. *However, this trial was previously reviewed by OCP and found acceptable. Therefore, additional requests for data will not be made in this regard.*

Inspections: Clinical trial 150075 will need inspection as it provides pivotal support to approval; Trial AA24171 was previously submitted to NDA 22032 and study conduct/bioanalysis was by [REDACTED] ^{(b) (4)} with a history of bioanalytical issues at that time]; At the time of approval of NDA 22032 in 2007, it appears that [REDACTED] ^{(b) (4)} site was inspected in regards to study AA24171 and OCP reviewers found that the issues in form 483 were sufficiently addressed [see review in DARRTs under NDA 22032 dated 06/01/2007 by Drs. Abi Adebawale and Sue Chih Lee]. Also see initial Clinical Pharmacology review for NDA 22032 dated 12/7/2006 at drugs@fda.

From the summary review of NDA 22032 at drugs@fda [Drs. Andrea Leonard-Segal and Joyce Korvick]:

Clinical Pharmacology:

“Refer to the review by Drs. Adebawale and Lee, dated June 1, 2007 and the e-mail exchange between Dr. Adebawale and Dr. Leonard-Segal entered into the Division Files System on June 5, 2007. The concerns related to the integrity of the Clinical pharmacology data have been resolved. The sponsor submitted pharmacokinetics and statistical data that demonstrates the bioequivalence of their omeprazole delayed release 20 mg formulation with Prilosec OTC 20.6 mg omeprazole magnesium delayed release tablets”.

Bridging Summary: The sponsor is attempting to bridge their proposed ODT formulation to formulation approved under NDA 21229 (Prilosec DR tablets OTC) by means of the following two trials.

Study 150075: Bridge between Dexcel's proposed 20 mg DR ODT tablet (Test; with or without water) vs. Dexcel's approved 20 mg DR tablet for OTC (Reference; NDA 22032); study conducted in 2015

Study AA24171: Bridge between Dexcel's approved 20 mg DR tablet for OTC (Test) vs. Astrazeneca's Prilosec OTC (Reference; NDA 21229); study conducted in 2005 *[reviewed and found acceptable by OCP in 2006/2007 as part of NDA 22032 review]*

Source of Information	Information Provided
Study 150075	Pharmacokinetic profile of Omeprazole OTD from oral administration with and without water compared to Omeprazole DR; Scientific “bridge” to reliance upon Omeprazole DR (NDA 022032); Information to rely upon
Study AA24171	Pharmacokinetic profile of Omeprazole DR from oral administration with and without water compared to Prilosec OTC; Scientific “bridge” to reliance upon Prilosec OTC (NDA 021229); Information to rely upon

Sponsor notes that “The approach to conduct the bioequivalence study using Omeprazole DR as reference drug and to cross reference to study AA24171 was discussed with FDA during the Pre-IND meeting held on 6 October 2015 (Reference ID: 3842047) and during the Pre-NDA meeting held on 9 May 2016 (Reference ID: 3927950).” Based on the meeting minutes the bridging approach appears to have been found acceptable by the review team.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
10/26/2016

SUE CHIH H LEE
10/26/2016