CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208025Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 208025	Submission Date(s): 08/06/2015
Brand Name	TBD
Generic Name	Lansoprazole
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	DCPIII
OND Division	DNDP
Sponsor	Camargo Pharma Services for Dexcel Pharma Technologies, Ltd
Submission Type; Code	Resubmission; 505b(2) NDA
Formulation; Strength(s)	Delayed Release, Orally Disintegrating Tablets, 15 mg USP
Indication	Treatment of frequent heart burn (OTC)

Reference ID: 3931639

This memo is to clarify that the reference product used for relative bioavailability/ bioequivalence assessments for the proposed lansoprazole ODT formulation in this 505 b(2) NDA 208025, was Prevacid 24 HR. The Clinical Pharmacology review in DARRTs (dated 04/20/2016) mentions this to be the reference formulation on several occasions, but also mistakenly noted the reference product to be Nexium 24 HR in three different places of the review (on pages 2 and 6).

In addition, the original OCP review recommendation to dose the proposed ODT formulation at least 30 minutes before eating has also been since reconsidered, and the sponsor's proposed language to (b) (4) before eating' is now found adequate.

This was communicated via email to DNDP on May 02, 2016, and the rationale was as follows [verbatim as noted in our email]:

"It appears that for the earlier approvals (original prescription prevacid and prevacid 24 hr), the dose was administered in the clinical trials 'before eating or before breakfast' in the morning and therefore labeled as such, without any further elaboration on time specification. The 70 % lower AUC when taken with a high-fat, high calorie meal for the proposed product also appears to be consistent to that noted for the approved prescription Prevacid. Therefore, it appears reasonable to not alter the label for the new ODT in this regard, and to accept the sponsor's labeling language to 'take (b) (4) before eating', as this is consistent with other labels and based on precedence. We will not be making any further labeling edits in this regard".

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
05/16/2016

SUE CHIH H LEE
05/16/2016
This is an addendum to the review dated 4/20/16.

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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Table of Contents

Reference ID: 3919697

1 Executive Summary

1.1 Recommendation

The application has been reviewed by the Office of Clinical Pharmacology and found to be acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Regulatory Background

This is a resubmission of a 505 b (2) NDA by Dexcel Pharma Technologies Ltd (DPT), for an orally disintegrating tablet (ODT) formulation of lansoprazole 15 mg for over-the-counter (OTC) use. The proposed indication is for the over-the-counter treatment of frequent heartburn. Lansoprazole Delayed-Release ODT is comprised of (b) (4) pellets containing the active substance, Lansoprazole, mixed with excipients to form a tablet which disintegrates when placed on the tongue.

The NDA was first submitted on 12/05/2014 and received refuse-to-file action on 02/06/2015 due to clinical safety related deficiencies. On 08/06/2015 the sponsor resubmitted the application with the requested information. The Sponsor intends to rely upon the Agency's findings of safety and efficacy for the OTC listed drug (LD), Prevacid® 24 HR (lansoprazole, delayed-release 15 mg capsule; Novartis, NDA 22327), along with information from the public domain, to support the approval of this application. DPT has conducted a bioequivalence study (Project 120383) to provide the scientific "bridge" to the agency's finding of safety and efficacy for Prevacid 24 HR and a comparative food-effect bioavailability study (Project 120384).

Relative bioavailability study 120383: The objectives of this study were to compare the rate and extent of absorption of lansoprazole delayed-release ODT 15 mg given without and/or with water (treatments A and B), or ODT swallowed intact with water (treatment C) versus Prevacid® 24HR (Reference; treatment D), 15 mg delayed-release capsule under fasting conditions. Using the average bioequivalence approach for statistical analysis, all parameters were within bioequivalence limits, except for the lower 90 % confidence bound for Cmax during treatment B which was slightly below the regulatory threshold of 80 %. This small deviation is not considered to be clinically meaningful. Overall, the study data suggests that under the conditions evaluated namely, test ODT without water (A), test ODT, followed by water (B), test ODT swallowed intact with water (C), the new lansoprazole formulation provided bioequivalent exposures compared to approved Nexium 24 HR 15 mg delayed release OTC capsule.

Reference ID: 3919697

Food-effect relative bioavailability study 120384: The objective of this study was to evaluate the effect of concomitant food intake on the pharmacokinetics of lansoprazole from the new delayed release ODT formulation. Test drug was dosed with or without a high fat, high calorie breakfast that was initiated 30 minutes prior to the dose. A significant food-effect (decreased exposure) on lansoprazole PK was noted, with fed/fasted ratios of 16.56 %, 23.61 % and 30.58 % for Cmax, AUCt and AUCinf, respectively.

Alcohol dose-dumping: *In vitro* alcohol dose dumping study conducted in presence of various strengths of alcohol (0 %, 5 %, 10 %, 20 %, and 40 %) in 0.1 N HCl showed significant dose dumping at 40 % alcohol but not at the lower strengths. The reference Prevacid 24 HR also showed complete release in presence of 40 % alcohol. Because lansoprazole is acid-labile, early release will result in degradation of drug in the acidic environment of the stomach and therefore potential loss of efficacy. Based on our assessment, an in vivo alcohol drug interaction study is not needed for this delayed release formulation given that 1) this is unlikely to be a safety concern, as the acid-labile lansoprazole will be degraded upon early release, likely resulting in an ineffective dose 2) early release of dose only occurred in vitro at the highest concentration tested (i.e. 40 % alcohol) which is not typically seen in common alcoholic beverages such as beer, wine etc.), and 3) target patients should in general avoid consumption of alcohol to prevent exacerbation of their heartburn. This issue was discussed via email on October 08, 2015 with DCP3 management (Dr. Edward D. Bashaw and Dr. Hae Young Ahn) and they concurred that an in vivo alcohol DDI study will not be needed.

Inspection: In a memo dated 11/10/2015, the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended accepting data without an on-site inspection due to recent good outcomes from the inspections of the clinical and bioanalytical sites involved in the pivotal bioequivalence trial.

2 Review of Relative Bioavailability Study 120383

Title: Randomized, Open-Label, 4-Way Crossover Design, Bioequivalence Study of lansoprazole Delayed-Release Orally Disintegrating Tablet 15 mg (Dexcel Pharma Technologies Ltd.) and Prevacid® 24HR (Reference) Following a 15 mg Dose in Healthy Subjects Under Fasting Conditions

Study objectives: To compare the rate and extent of absorption of lansoprazole delayed-release ODT 15 mg given with and/or without water, or swallowed with water versus Prevacid® 24HR (Reference), 15 mg delayed-release capsule under fasting conditions.

Study design: A single center, randomized, single-dose, open-label, 4-way crossover study in 72 healthy male and female volunteers; treatments are separated by washout periods of seven days.

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Treatments:

Treatment A: 1 x 15 mg delayed-release ODT placed on the tongue until disintegration and then swallowed without water;

Treatment B: 1 x 15 mg delayed-release ODT placed on the tongue until disintegration and then swallowed with water;

Treatment C: 1 x 15 mg delayed-release ODT swallowed with water;

Treatment D (Reference): 1 x 15 mg delayed-release capsule (Prevacid® 24HR) swallowed with water.

Randomization sequences: Subjects were to be randomized equally into one of the following sequence groups: ADBC, BACD, CBDA, or DCAB.

PK sampling: Blood samples were collected prior to study drug administration and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 5.0, 6.0, 9.0, and 12 hours post-dose in each period.

Analytical method: A validated HPLC-MS/MS method was used to analyze plasma lansoprazole concentrations. The method was validated over 2 to 1000 ng/mL range and demonstrated adequate accuracy and precision. Freeze-thaw stability was established for 4 cycles, and long-term stability established for 179 days. Validation parameters and incurred sample reproducibility during sample runs were also found to be reasonable.

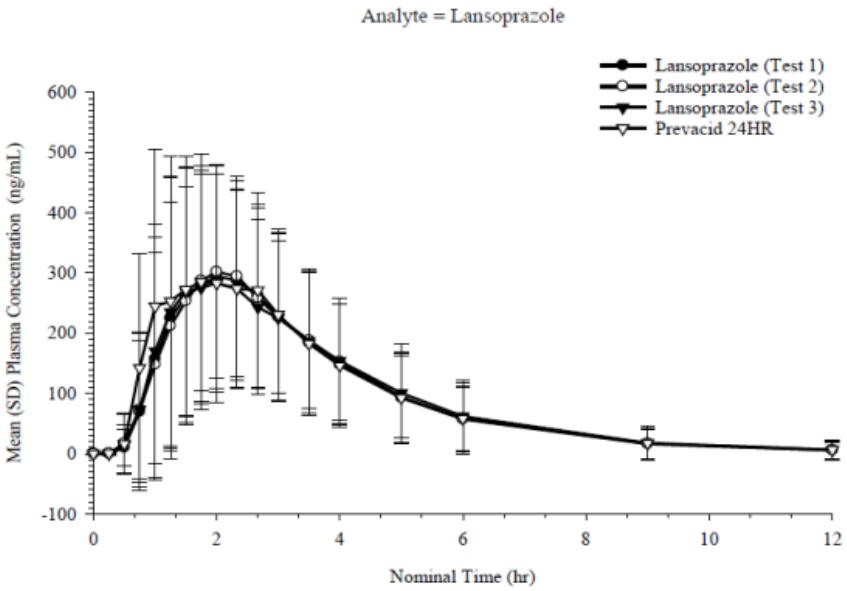
PK analyses*:* Plasma concentration-time data was subjected to non-compartmental PK analysis by reviewer using Pharsight Phoenix. PK parameters assessed included AUC0-t, AUC0-inf, Cmax, Tmax, T1/2, and Kel.

Statistical methods: For bioequivalence, the 90% geometric confidence intervals of the test treatment ratios (relative to reference D) of least squares means from the ANOVA of the ln-transformed AUC0-t, AUC0-inf and Cmax should be within 80.00% to 125.00%.

Results:

Lansoprazole mean plasma concentration-time profiles are as shown:

Reference ID: 3919697



Pharmacokinetic parameters generated by sponsor using non-compartmental PK analyses of the lansoprazole plasma concentration-time data are summarized below:

Mean ± SD (CV%)	Plasma Lansoprazole			
	Lansoprazole (Test 1)	Lansoprazole (Test 2)	Lansoprazole (Test 3)	Prevacid 24HR
N	68[1]	66[2]	62[3]	69[4]
AUC_{0-t} (ng•hr/mL)	1075.35 ± 612.46 (56.95)	1084.08 ± 608.96 (56.17)	1098.38 ± 559.75 (50.96)	1131.75 ± 671.24 (59.31)
AUC_{0-inf} (ng•hr/mL)	1101.88 ± 649.91 (58.98)	1110.30 ± 651.39 (58.67)	1128.70 ± 602.76 (53.40)	1161.76 ± 722.33 (62.18)
Residual Area (%)	2.04 ± 2.92 (142.88)	1.83 ± 2.17 (118.63)	1.96 ± 3.15 (160.57)	2.08 ± 3.87 (186.47)
C_{max} (ng/mL)	444.18 ± 178.17 (40.11)	420.34 ± 157.02 (37.36)	447.41 ± 151.29 (33.81)	476.21 ± 186.09 (39.08)
T_{max}[a] (hr)	1.75 (0.750 - 4.00)	2.00 (0.750 - 5.00)	1.75 (0.750 - 5.00)	1.50 (0.750 - 5.00)
K_{el} (1/hr)	0.6124 ± 0.2216 (36.19)	0.6089 ± 0.2139 (35.13)	0.5984 ± 0.2010 (33.59)	0.5955 ± 0.2073 (34.81)
$T_{½ el}$ (hr)	1.30 ± 0.56 (43.04)	1.31 ± 0.56 (43.10)	1.33 ± 0.60 (45.33)	1.35 ± 0.62 (45.75)

[a] Median
(Min - Max)

Statistical analyses:

Relative bioavailability: Results of average BE analysis (reviewer analyses using SAS 9.3) are shown below:

	Test A vs. Ref D	Test B vs. Ref D	Test C vs. Ref D
CMAX	92.67 [83.59 – 102.74]	87.60 [78.96 – 97.19]	95.08 [85.58 – 105.64]
AUCT	94.84 [88.39 – 101.76]	93.91 [87.48 – 100.81]	97.94 [91.13 – 105.25]
AUCINF	94.75 [88.54 – 101.39]	93.65 [87.47 – 100.27]	97.70 [91.16 – 104.71]

A: Test ODT without water; B: Test ODT, followed by water; C: Test ODT swallowed intact with water; D: Reference; Nexium 24 HR

With the exception of Cmax for treatment B, all 90 % confidence bounds for the T/R LSM ratios for different conditions of use (A, B, C) were within 80- 125 % limits for bioequivalence. For treatment B (i.e. test drug allowed to disintegrate on the tongue and swallowed, followed by 250 mL water), the lower 90 % confidence bound for Cmax was slightly below the regulatory threshold of 80 %. The AUCs were however within BE ranges for all treatments. The observed modest decrease (relative to reference D) in Cmax for treatment B is unlikely to have any clinical implications, especially given that the AUC parameters were bioequivalent.

Conclusions: Data suggests that under the conditions evaluated namely, test ODT without water (A), test ODT followed by water (B), test ODT swallowed intact with water (C), the new lansoprazole formulation provided bioequivalent exposures compared to approved Nexium 24 HR 15 mg delayed release OTC capsule.

3 Review of Food-Effect Relative BA Study 120384

Title: Randomized, open-label, 2-way crossover design, comparative bioavailability, food-effect study of lansoprazole delayed release orally disintegrating tablet 15 mg

Study objectives: To assess the effect of food on the pharmacokinetics of lansoprazole delayed release ODT formulation.

Study design: This was a single center, randomized, single-dose, open-label, 2-way crossover comparative BA study to compare the rate and extent of absorption of a test

Lansoprazole under fasting and fed conditions in N = 18 healthy adult subjects, 18 years of age or older.

Treatments: For the 'fed treatment' A, after a supervised overnight fast of at least 10 hours, subjects were to be served a high-fat, high-caloric breakfast 30 minutes before drug administration. Subjects were dosed as specified in the protocol and subsequently fasted for a period of at least 4 hours. For the fasted treatment B, subjects were required to fast for at least 10 hours overnight and for 4 hours after dose. Subjects were required to place the ODT tablet on their tongue until it disintegrates completely and then swallow it. No water was allowed.

PK sampling: In each period, blood samples were drawn into blood collection tubes containing (EDTA) K2 prior to drug administration and 0.5, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 7.00, 8.00, 10.0, and 12.0 hours post-dose, in each period. Actual sampling times were used for statistical analyses.

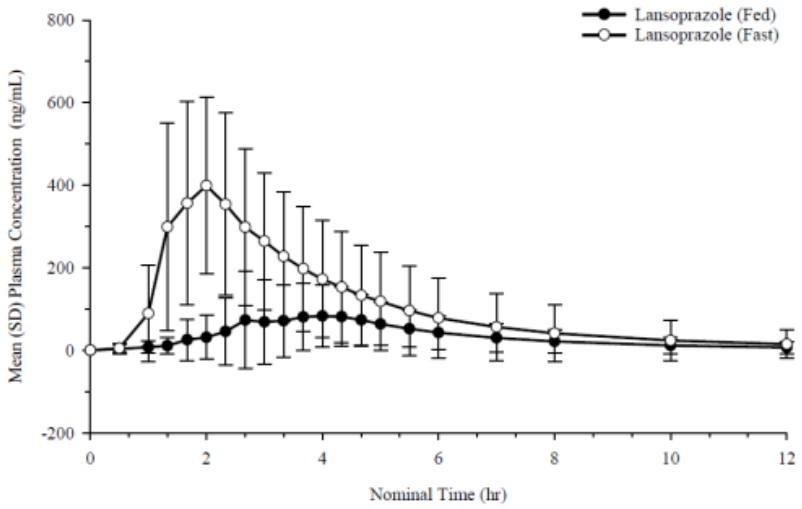
Analytical method: A validated HPLC-MS/MS method was used to analyze plasma lansoprazole concentrations. The method was validated over 2 to 1000 ng/mL range and demonstrated adequate accuracy and precision. Freeze-thaw stability was established for 4 cycles, and long-term stability established for 179 days. Validation parameters and incurred sample reproducibility during sample runs were also found to be reasonable.

PK and Statistical methods: The following PK parameters were calculated by standard non-compartmental methods for lansoprazole: AUC0-t, AUC0-inf, Cmax, Tmax, T1/2, and Kel. The ratios of means (Fed-to-Fasted, A/B) and 90% geometric confidence intervals for the ratio of means, based on least-squares means from the ANOVA of the ln-transformed data, were calculated for AUC0-t, AUC0-inf, and Cmax. The absence of food-effect on PK was to be confirmed if the 90% geometric C.I. of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC0-inf, AUC0-t, and Cmax were within 80.00% to 125.00%.

Results:

Mean plasma lansoprazole- time curves are shown for the fed and fasted groups of the test formulation:

Reference ID: 3919697



Mean plasma lansoprazole pharmacokinetic parameters are summarized by sponsor for the test ODT formulation under fed and fasted conditions:

Mean ± SD (CV%)	Plasma Lansoprazole	
	Lansoprazole (Fed)	Lansoprazole (Fast)
N	17	17
AUC_{0-t} (ng•hr/mL)	397.28 ± 368.94 (92.87)	1325.20 ± 994.34 (75.03)
AUC_{0-inf} (ng•hr/mL)	460.39 ± 429.12 (93.21)[b]	1452.47 ± 1185.92 (81.65)[b]
Residual Area (%)	9.14 ± 10.70 (117.04)[b]	2.75 ± 4.64 (168.57)[b]
C_{max} (ng/mL)	122.84 ± 115.95 (94.39)	485.94 ± 221.19 (45.52)
T_{max}[a] (hr)	4.33 (2.33 - 8.08)	1.67 (1.33 - 3.00)
K_{el} (1/hr)	0.4471 ± 0.2052 (45.88)[b]	0.5341 ± 0.2063 (38.63)[b]
$T_{½ el}$ (hr)	2.20 ± 1.79 (81.70)[b]	1.60 ± 0.96 (59.87)[b]

[a] Median
(Min - Max)

[b] N=16, Subject 17 not included in calculation of summary statistics
Profile of Subject 7 was excluded

Statistical analysis: Reviewer calculation of PK by non-compartmental analysis, followed by average bioequivalence analysis using Pharsight Phoenix, provided the following results, comparable to the sponsor's output:

Reference ID: 3919697

Parameter	Fed/Fasted (%) [90 % confidence interval]
Cmax	16.56 [10.51 – 26.11]
AUCT	23.61 [16.48 – 33.83]
AUCINF	30.58 [21.50 – 43.51]

Conclusions: As expected for lansoprazole, significant food-effect (i.e. decrease in systemic exposure in presence of food) was noted for the test formulation. Overall, significant food-effect on lansoprazole PK from delayed release ODT formulation supports dosing of the new formulation before food intake.

4 Labeling Recommendations

- Label recommends dosing the new lansoprazole delayed release ODT with or without water, or alternatively swallowed intact with water. This is supported by data from the pivotal bioequivalence trial and therefore acceptable.

- Label recommends dosing before eating in the morning. We recommend the following revision due to the observed substantial decrease in systemic lansoprazole exposure in presence of food (~ 83 % decrease in Cmax and ~ 70 % % decrease in AUC). The proposed revision is also expected to improve patient's understanding and therefore compliance with the recommendation to dose tablet on an empty stomach:

  From: take 1 tablet before eating in the morning
  To: take 1 tablet at least 30 minutes before eating in the morning

- Label states 'do not take this medicine with alcohol'. This is acceptable due to potential for loss of efficacy with alcohol, particularly at higher alcohol strength.

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
04/20/2016

SUE CHIH H LEE
04/20/2016

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 208025

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**208025**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**Lansoprazole**
Medical Division	**DNDP**	**Drug Class**	**Proton Pump Inhibitors**
OCP Reviewer	**Sandhya Apparaju, Ph.D.**	**Indication(s)**	**Treatment of Frequent Heartburn (over-the-counter)**
OCP Team Leader	**Sue Chih Lee, Ph.D.**	**Dosage Form**	**Delayed Release, Orally Disintegrating Tablets, 15 mg USP**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Once daily before eating in the morning for 14 d**
Date of Re-Submission	**08/06/2015**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**April 26, 2016**	**Sponsor**	**Camargo Pharma Services, for Dexcel Pharma Technologies Ltd**
Medical Division Due Date	**April 26, 2016**	**Priority Classification**	**Standard**
PDUFA Due Date	**June 7, 2016**	**Regulatory Pathway**	**505b(2); Reference Drug: Prevacid 24h (NDA 22327)**

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 208025

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 208025

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		**Study 120383 Proposed ODT vs. reference drug (Prevacid 24HR)**
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		**Study 120384 (proposed drug in fed vs, fasted conditions)**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	**X**			**ONDQA Biopharm will review this in vitro data**
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**			**Waiver requested**
Literature References				
Total Number of Studies	**X**	**2**		**Phase I BE and food-effect trials in healthy volunteers**

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Reference drug Prevacid 24 HR
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 208025

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 208025

	validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?	X			505b(2) Prevacid 24 HR
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	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)?			X	505b(2) NDA; refer to PREVACID 24 HR
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	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?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
Pending; see internal comments below

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 208025

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 208025

Internal comments: The sponsor has submitted results of an in vitro alcohol dissolution study, which showed early release of lansoprazole from this delayed release formulation in presence of 40 % alcohol, but not at 5%, 10 % or 20 % alcohol. Sponsor at this time proposes to address this via labeling language to not administer dose with alcohol. The biopharmaceutics team in ONDQA will review the results from this *in vitro* investigation during the current NDA review cycle. Based on the preliminary (filing review) input provided by that group to the review team, the findings related to early release of dose, potentially due to compromised (b) (4) of the formulation may warrant OCP to address this matter further. Particularly, it needs to be addressed whether a follow-up *in vivo* alcohol interaction study in volunteers, at one or more strengths of alcohol would be needed to appropriately label the product. This matter is currently under consideration, and if a path forward has been identified it will be communicated to the project manager for incorporation into the 74-day letter or will be sent out as a separate advice letter to the sponsor.

Filing memo:

Dexcel Pharma Technologies Ltd. (referred to as DPT or the Sponsor) submits this new drug application (NDA) for over the counter (OTC) Lansoprazole Delayed-Release (DR) orally disintegrating tablet (ODT) 15 mg utilizing the 505(b)(2) regulatory pathway. The proposed indication is for the treatment of frequent heartburn. The Sponsor intends to rely upon the Agency's findings of safety and efficacy for the OTC listed drug (LD), Prevacid® 24 HR (lansoprazole, delayed-release 15 mg capsule; Novartis, NDA 22327), in conjunction with information from the public domain, to support the approval of this application. DPT has conducted a bioequivalence study (Project 120383) and a comparative bioavailability study (Project 120384) to provide the scientific "bridge" to the agency's finding of safety and efficacy for Prevacid 24 HR.

The product is described as follows: "Lansoprazole Delayed-Release Orally Disintegrating Tablets (ODT), are comprised of (b) (4) pellets containing the active substance, Lansoprazole, mixed with excipients to form a tablet which disintegrates when placed on the tongue".

Included in this Initial NDA submission are complete study reports for two studies conducted in healthy volunteers:

• Project 120383: a single center, randomized, single-dose, open-label, 4-way crossover BE study to compare the rate and extent of absorption of DPT's lansoprazole with and/or without water, versus the LD Prevacid 24HR under fasting conditions. A total of 72 healthy adult subjects were included in this study.

• Project 120384: a single center, randomized, single-dose, open-label, 2-way crossover comparative BA study to compare the rate and extent of absorption of a test lansoprazole under fasting and fed conditions. A total of 18 healthy adult subjects were included in this study.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 208025

Type of Study	Study Identifier	CTD Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	120383	5.3.1.2	compare reference and to-be-marketed formulation	crossover	Lansoprazole / 1 x 15 mg delayed-release orally disintegrating tablet / Oral	72	Healthy subjects	single dose	complete/ full
BA	120384	5.3.1.2	food effect	crossover	Lansoprazole / 1 x 15 mg delayed-release orally disintegrating tablet / Oral	18	Healthy subjects	single dose	complete/ full

Bioanalytical methods and datasets for the pivotal BE study 120383 and the food effect study 120384 could be located in the submission.

Pending review, results of the bioequivalence study were as follows:

			90% Geometric C.I.[2]			
Parameter	Treatment Comparisons	Ratio[1]	Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	Test 1(A)-Test 2(B)	101.16%	94.15%	108.69%	25.38%	57.47%
	Test 1(A)-Reference(D)	94.80%	88.33%	101.74%		
	Test 2(B)-Reference(D)	93.72%	87.25%	100.65%		
	Test 3(C)-Reference(D)	97.79%	90.90%	105.20%		
AUC_{0-inf}	Test 1(A)-Test 2(B)	101.39%	94.62%	108.63%	24.37%	58.24%
	Test 1(A)-Reference(D)	94.70%	88.48%	101.37%		
	Test 2(B)-Reference(D)	93.41%	87.21%	100.05%		
	Test 3(C)-Reference(D)	97.62%	91.00%	104.71%		
C_{max}	Test 1(A)-Test 2(B)	106.08%	95.47%	117.85%	37.89%	26.82%
	Test 1(A)-Reference(D)	92.57%	83.45%	102.68%		
	Test 2(B)-Reference(D)	87.26%	78.59%	96.90%		
	Test 3(C)-Reference(D)	95.15%	85.50%	105.90%		

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Source: CSR Project 120383, Table 11.4.2.3-3

Treatments A: 15-mg DR ODT placed on the tongue until disintegration and then swallowed without water;
Treatment B: 15-mg DR ODT placed on the tongue until disintegration and then swallowed with water;
Treatment C: 15-mg DR ODT swallowed with water
Treatment D [Reference]: 15-mg DR Prevacid 24 HR capsule swallowed with water

DPT believes that the conducted bioequivalence and bioavailability studies provide the scientific "bridge" to the LD across all dosing regimens and proposes to include the dosing regimens of disintegration on the tongue and subsequent swallowing with or without water, as well as swallowing the tablet whole with water in the proposed labeling.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 208025

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 208025

Pending review, dosing with food demonstrated significant decrease in systemic exposure of lansoprazole from the ODT formulation: fed/fasted ratios of 23.25%, 27.03% and 16.56% respectively for AUC0-t, AUC0-inf, and Cmax. The product is proposed to be administered prior to a meal in the morning as noted in the proposed labeling text.

Validation and Bioanalytical reports (pivotal BE study 120383):

Method validation:

The Sponsor employed a fully validated method using HPLC-mass spectrometry (MS)/MS (API 4000) with an automated extraction method for the detection of lansoprazole concentrations in human plasma samples during the drug development program. This analytical detection method was utilized for analysis of lansoprazole plasma concentrations in Project 120383 and Project 120384.

(b) (4) developed and validated an HPLC method using tandem mass spectrometry detection and automated extraction for the analysis of lansoprazole in human EDTA K_2 plasma over a concentration range of 2 to 1000 ng/mL (Validation Report 105051AATQ). Additional partial validation reports were issued to address post-preparative stabilities at 4°C and at room temperature (Partial validation report 1), method robustness (Partial validation report 2), potentially interfering drugs (levonorgestrel, ethinyl estradiol, cotinine, and salycilic acid), matrix selectivity and matrix effect (Partial validation report 3), and modification of the calibration curve range (Partial validation report 4).

VALIDATION OF A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD USING TANDEM MASS SPECTROMETRY DETECTION AND AUTOMATED EXTRACTION FOR THE DETERMINATION OF LANSOPRAZOLE IN HUMAN EDTA K_2 PLASMA

Project Number: 105051AATQ

Method Developed by:

(b) (4)

July 27, 2010

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(b) (4)

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 208025

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 208025

Bioanalytical report:

RANDOMIZED, OPEN-LABEL, 4-WAY CROSSOVER DESIGN, BIOEQUIVALENCE STUDY OF LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLET 15 mg (Dexcel Pharma Technologies Ltd.) AND PREVACID® 24HR (REFERENCE) FOLLOWING A 15 mg DOSE IN HEALTHY SUBJECTS UNDER FASTING CONDITIONS

FINAL BIOANALYTICAL REPORT
Version 01
Date: 03-JUN-2014

Contract Research Organization:
(b) (4)

Sponsor:

Dexcel Pharma Technologies Ltd.

1 Dexcel St
Or-Akiva, 3060000
Israel

Sponsor's Representatives:

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Study Phase: Bioequivalence

(b) (4)

Inspection: An OSIS inspection of the clinical and bioanalytical facilities for the pivotal BE study 120383 will be requested.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 208025

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
09/25/2015

SUE CHIH H LEE
09/25/2015