CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208025Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 21, 2016
From	Francis E. Becker, M.D., F.A.C.P.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 208025 SD-5
Applicant	Dexcel Pharma Technologies Limited
Date of Submission	August 6, 2015
PDUFA Goal Date	June 7, 2016
Proprietary Name / Non-Proprietary Name	(Proprietary name not determined)/lansoprazole delayed release orally disintegrating tablets
Dosage form(s) / Strength(s)	Delayed-release orally disintegrating tablets / 15 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of frequent heartburn (occurs 2 or more days a week) in adults ≥18 years of age
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of frequent heartburn (occurs 2 or more days a week) in adults ≥18 years of age

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dexcel Pharma Technologies Ltd (DPT) submitted 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. Lansoprazole is a commonly used member of the proton-pump inhibitor (PPI) class of drugs which increase intragastric pH, relieving the symptoms of acid-related disorders. Similar to all PPIs, it has been shown to be highly effective for suppressing intra gastric acidity and providing 24-hour relief (Blum, 1997). The proposed indication is for the treatment of frequent heartburn (occurs 2 or more days a week) in patients 18 years of age and older. I recommend approval of this product for the proposed indication. Lansoprazole delayed release ODT will provide consumers with a convenient option for OTC treatment of frequent heartburn. The ODT formulation will provide an alternative mode of administration based on consumer preference.

Heartburn is a condition which, although not life threatening, is very prevalent in the United States and results in significant morbidity, including

pain, lack of sleep, dietary restrictions, and decreased work productivity. Approximately 18- 28% (El-Serag, 2014) of individuals in the United States have gastrointestinal reflux disease (GERD), of which heartburn is a symptom. Available OTC treatment options include antacids (aluminum and/or magnesium hydroxide, calcium carbonate, and sodium bicarbonate), histamine$_2$ receptor agonists (H_2RAs; famotidine, ranitidine, cimetidine, and nizatidine), and other PPIs, including lansoprazole delayed release capsule 15 mg (Prevacid 24 HR), omeprazole (Priolsec OTC), combination of omeprazole and sodium bicarbonate (Zegerid OTC), and esomeprazole magnesium (Nexium 24 HR). Proton-pump inhibitors are generally accepted as being amongst the most effective medicines for the relief of heartburn.

The sponsor conducted two pharmacokinetic studies in support of this application. In a single-center, randomized, single-dose, open-label, 4-way crossover study (**Project 120383**) conducted in 72 healthy male and female volunteers, the rate and extent of absorption of lansoprazole delayed-release ODT 15 mg given without and/or with water, or ODT swallowed intact with water was found to be comparable (bioequivalent) to the listed drug, Prevacid 24 HR 15 mg delayed-release capsule, under fasted conditions. Prevacid 24 HR 15 mg delayed release capsule is currently approved for OTC use for treatment of frequent heartburn (occurs 2 or more days a week) in adults ≥18 years of age, based on the results of three clinical trials that demonstrated efficacy of lansoprazole in the treatment of frequent heartburn. Since lansoprazole delayed-release ODT 15 mg was demonstrated to be bioequivalent to Prevacid 24 HR 15 mg delayed-release capsule, it can be concluded that it will be effective for the same indication.

In addition, a food effect study (**Project 120384**) was conducted and, as expected for lansoprazole, demonstrated significant food-effect (i.e. decrease in systemic exposure in presence of food) for the proposed drug product. Overall, significant food-effect on lansoprazole PK from delayed release ODT formulation supports dosing of the new formulation before food intake.

In the two pharmacokinetic studies conducted by the sponsor in support of this application, adverse events were generally mild, reversible, and infrequent, and were consistent with the known safety profile of lansoprazole. The safety of lansoprazole was further supported by safety data from 3 pivotal clinical studies (1138 patients) identified in the published literature that were conducted to support the approval of the listed drug (LD), Prevacid 24 HR (**NDA 22327**). The approved prescription Prevacid (lansoprazole delayed release capsule, 15 mg. 30 mg, **NDA 20406**) labeling states that over 10,000 patients have been treated with Prevacid in Phase 2 or 3 clinical trials involving various doses and durations of treatment (Takeda Pharmaceuticals America, 2014). In addition extensive postmarketing safety data was submitted with this application. The most frequent adverse events include diarrhea, headache, abdominal pain, nausea, and constipation. The sponsor conducted oropharyngeal evaluations in the two pharmacokinetic studies (**Project 120383** and **Project 120384)** to assess the safety of lansoprazole ODT due to its orally disintegrating drug delivery technology. Minimal, if any, oropharyngeal irritation was observed during the conduct of these studies.

Thus, the safety profile of the proposed product is expected to be comparable to that of the currently marketed Prevacid 24HR OTC product. Many of the more serious safety issues identified in prevacid prescription labeling are related to higher dosing and longer dosing regimens than proposed for OTC use. (b) (4) At present, there are no serious safety concerns identified for the proposed 14-day dosing with a 15 mg dose.

Overall, if taken as directed, the proposed lansoprazole drug product should be considered safe. Using the lower dose (15 mg) for the 14-day treatment regimen should alleviate frequent heartburn, while putting the patient at a low risk for infrequent and mild adverse events. Appropriate labeling including instructions to stop use and ask a doctor if you need to take this product for more than 14 days, and appropriate warnings and dosing instructions should effectively mitigate safety risks. Lansoprazole delayed-release ODT should be taken before eating and should not be taken with alcohol, because taking after eating or with a shot of alcohol will result in lower absorption of drug and thus will decrease efficacy. In addition, alcohol would worsen the underlying condition (heartburn) and therefore should not be used by consummers with heartburn. It is important to not chew or crush the tablets, because this will damage the pellets in the tablet and effect drug release, adversely impacting drug effectiveness. Consumers less than 18 years of age should not take OTC PPIs without consulting a doctor, because heartburn in children may indicate a serious medical condition requiring medical attention. Heartburn which persists despite OTC treatment requires evaluation by a health care provider, and consumers should ask a doctor before use if they have certain medical conditions (e.g., liver disease, heartburn for more than 3 months, chest pain or shortness of breath, wheezing, nausea or vomiting, or stomach pain), take certain medicaions which are known to interact with lansoprazole (e.g., warfarin, digoxin, theophylline), or are pregnant or breast feeding. All of these instructions and precautions will be included in the Drug Facts Label (DFL). With the exception of instructions such as to not chew or crush the tablets that are unique to the ODT formulation, these directions and precautions will be identical to the Prevacid 24 HR ccapsule DFL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Treatment of frequent heartburn (occurs 2 or more days a week) in adults ≥18 years of age. Approximately 18- 28% of individuals in the United States have gastrointestinal reflux disease (GERD), of which heartburn is a symptom. • Although the condition is not life-threatening, heartburn may be associated with pain, dietary restrictions, disruptions in sleep, and decreased work productivity.	Heartburn is a condition which, although not life threatening, is very prevalent in the United States and results in significant morbidity, including pain, lack of sleep, and decreased work productivity.
Current Treatment Options	Available over-the-counter treatment options include • antacids to neutralize stomach acid such as aluminum and/or magnesium hydroxide, calcium carbonate, and sodium bicarbonate • H_2RAs to block acid sevretion such as famotidine, ranitidine, cimetidine, and nizatidine • PPIs to block acid secretion including omeprazole (Priolsec OTC), lansoprazole (Prevacid 24 HR), combination of omeprazole and sodium bicarbonate (Zegerid OTC), and esomeprazole magnesium (Nexium 24 HR).	Lansoprazole is a commonly used member of the proton-pump inhibitor (PPI) class of drugs, which increase intragastric pH, relieving the symptoms of acid-related disorders. Similar to all PPIs, it has been shown to be highly effective for suppressing intra gastric acidity and provide 24-hour relief (Blum, 1997). Proton-pump inhibitors are generally accepted as being amongst the most effective medicines for the relief of heartburn (Tack, 2010) and approved as an over the counter medicine for the treatment of frequent heartburn.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	In a single-center, randomized, single-dose, open-label, 4-way crossover study (**Project 120383**) conducted in 72 healthy male and female volunteers, the rate and extent of absorption of lansoprazole delayed-release ODT 15 mg given without and/or with water, or ODT swallowed intact with water was found to be comparable (bioequivalent) to the listed drug, Prevacid 24 HR 15 mg delayed-release capsule under fasted conditions. In addition, a food effect study was conducted and, as expected for lansoprazole, demonstrated significant food-effect (i.e. decrease in systemic exposure in presence of food) for the proposed drug product. Overall, significant food-effect on lansoprazole PK from delayed release ODT formulation supports dosing of the new formulation before food intake.	Prevacid 24 HR 15 mg delayed release capsule is currently approved for OTC use for treatment of frequent heartburn (occurs 2 or more days a week) in adults ≥18 years of age, based on the results of three clinical trials that demonstrated efficacy of lansoprazole in the treatment of frequent heartburn. Since lansoprazole delayed-release ODT 15 mg was demonstrated to be bioequivalent (**Project 120383**) to Prevacid 24 HR 15 mg delayed-release capsule, it can be concluded that it will be effective for the same indication. The ODT formulation will provide an alternative mode of administration based on consumer preference.
Risk	In the two pharmacokinetic studies conducted by the sponsor in support of this application, adverse events were generally mild, reversible, and infrequent, and were consistent with the known safety profile of lansoprazole. The safety of lansoprazole was further supported by safety data from 3 pivotal clinical studies (1138 patients) identified in the published literature that were conducted to support the approval of the LD, Prevacid 24 HR (**NDA 22327**). The approved Prevacid (lansoprazole delayed release capsule, 15 mg. 30 mg, **NDA 20406**) labeling states that over 10,000 patients have been treated with Prevacid in Phase 2 or 3 clinical trials involving various doses and durations of treatment (Takeda Pharmaceuticals America, 2014), and there is extensive postmarketing safety data. The most frequent adverse events include diarrhea, headache, abdominal pain, nausea, and constipation. The sponsor conducted oropharyngeal studies to assess the safety of lansoprazole ODT due to its orally disintegrating drug delivery technology. The oropharyngeal observations made during the conduct of the studies suggest the proposed product can be safely administered to the general population.	The safety profile of the proposed product is expected to be comparable to that of the currently marketed Prevacid 24HR OTC product. Many of the safety issues identified in prescription labeling are related to higher dosing and longer dosing regimens (b) (4) [redacted] At present, there are no serious safety concerns identified for the proposed 14-day dosing with a 15 mg dose.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	Serious safety concerns regarding lansoprazole use are related to higher doses, and longer dosing durations than what is intended for the proposed product.	Overall, if taken as directed, the proposed lansoprazole drug product should be considered safe. Using the lower dose (15 mg) for the 14-day treatment regimen should alleviate frequent heartburn, while putting the patient at a low risk for infrequent and mild adverse events. Appropriate labeling including instructions to stop use and ask a doctor if you need to take this product for more than 14 days and appropriate warnings and dosing instructions should effectively mitigate safety risks.

2. Background

Dexcel Pharma Technologies Ltd (DPT) submitted 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 heartburn in patients 18 years of age and older. 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) in conjunction with the public domain, to support approval of this application. DPT has conducted a bioequivalence study (**Study 120383**) and a comparative bioavailability study **(Study 12034**) to provide the scientific bridge to the safety and efficacy findings for Prevacid 24 HR. These are the only new studies conducted for this application.

In writing ths summary review, I have considered the following primary FDA reviews:

Table 1: Primary Reviews

Materials Reviewed	Name of Discipline Primary Reviewer
DMEPA Labeling Review	Grace P. Jones, PharmD, BCPS
DNDP Labeling Review	Mary R. Vienna, RN, MHA
DNDP Medical Officer Review	Ketan P. Parikh, M.D.
DNDP Pharmacology/Toxicology Review	Wafa Harrouk, Ph.D.
Office of Clinical Pharmacology Review	Sandhya Apparaju, Ph.D.
Quality Review Team Reviews	Swapan K. De, Ph.D. (see **Table 2**)

Lansoprazole is a proton pump inhibitor (PPI) and is currently marketed for various acid-related disorders in 92 countries. It was approved for prescription use in the United States in 1995 as Prevacid®. In the United States, it is indicated in adults for the treatment of gastroesophageal reflux disease (GERD), erosive esophagitis, gastric and duodenal ulcers, H. pylori eradication, and hypersecretory conditions including Zollinger-Ellison syndrome. Prescription labeling allows for adult oral doses ranging from 15 mg once daily to 30 mg twice daily for most indications (30 mg three times daily for 14 days is allowed for dual therapy with amoxicillin for H. pylori eradication to reduce the risk of duodenal ulcer recurrence).

The pediatric indications for prescription Prevacid are:

- 12-17 year olds: treatment of symptomatic GERD, erosive esophagitis, and hypersecretory conditions including Zollinger-Ellison Syndrome

- 1-11 years old: short-term treatment of symptomatic GERD, and short-term treatment of erosive esophagitis

PPIs and the proposed OTC indication are familiar to U. S. consumers. OTC omeprazole (Prilosec OTC), lansoprazole (Prevacid 24 HR), and esomeprazole (Nexium 24 HR) were approved in 2003, 2009, and 2014, respectively. The intended indication for OTC marketing of lansoprazole delayed-release ODT 15 mg is for the treatment of frequent heartburn (occurring 2 or more days a week) in adults age 18 or older. This indication is consistent with other OTC PPI labels. FDA has taken the position that symptoms of heartburn in children should be evaluated by a healthcare provider for safety reasons. The proposed dosing regimen is a daily oral dose of 15 mg for 14 days, with an option for a repeat 14-day course no sooner than 4 months. Thus, the proposed indication and dosing are identical to currently approved OTC Prevacid 24 HR.

During the sponsor's development program, there were several interactions with FDA under **IND 118528**. These interactions are reviewed in detail in the Clinical Review of Ketan Parikh, M.D., Medical Officer. Briefly, important interactions were as follows:

- 23 September, 2013: Type B Pre-IND Meeting: FDA agreed with the sponsor's proposed 505(b)(2) approach with reliance on safety and efficacy data from **NDA 022327** (Prevacid 24HR) and bioequivalence (BE) study bridging an approved product. The sponsor was advised to address food effect on pharmacokinetics (PK) for the proposed formulation and perform an *in vitro* alcohol-induced dose dumping study or provide justification as to why this is not feasible.
- 28 February 2014: Initial Pediatric Safety Plan (iPSP) submitted requesting full pediatric waiver.
- 11 December 2014: FDA approved the Pediatric Safety Plan (PSP)
- 05 December 2014: NDA submitted for lansoprazole delayed-release ODT
- 06 February 2015: Refuse-to-file (RTF) letter sent to sponsor due to numerous deficiencies including missing carton label and consumer information leaflet, absence of datasets for PK studies, absence of listing of countries where the product or active ingredient is marketed, absence of information as to whether the product or active ingredient was ever withdrawn due to safety concerns, and incomplete safety data (sources of all safety data not clearly identified; updated summary and analysis from FAERS, WHO, NPDS, and DAWN databases not provided; copies of all reference articles not provided; and case report forms for all subjects in PK studies not provided).
- 03 April 2015: Type A Meeting held with the sponsor. The filing deficencies were discussed and details of data to be submitted was agreed upon. FDA did not agree with single dose oropharyngeal assessments in proposed bioavailability (BA) studies since the proposed tablet is for repeated use. The sponsor was advised that if it chooses not to conduct an in vivo alcohol dose-dumping study, the lack of in vivo data would be a review issue, and the sponsor was advised that, in this case, it would ned to provide justification and address how the safety and/or efficacy of the product would be compromised when used with alcohol and how the sponsor plans to mitigate the risk. (b) (4) .

- 06 August 2015: The sponsor resubmitted the NDA.

3. Product Quality

Drug Formulation

Lansoprazole is a white to off-white (b) (4) powder and is a BCS Class II (high permeability, low solubility) drug. The proposed drug product consists of (b) (4) an orally disintegrating delayed release tablet, as shown schematically in **Figure 1** below (electronically copied and reproduced from the Drug Pruduct Review; Muthukumar Ramaswamy, Ph.D, March 20, 2016). The tablets will disintegrate within a minute when placed under the tongue. Since damage to the (b) (4) pellets would affect drug release, the sponsor has proposed appropriate tableting to avoid damage to (b) (4) pellets. (b) (4)

Figure 1: Lansoprazole Delayed-Release Orally Disintigrating Tablet – Schematic Representation

(b) (4)

The Lansoprazole DR ODT are packed in two 7-count (b) (4) 14-count (b) (4) push-through lidding foil or in a 14-count 45 mL high density polyethylene (HDPE) bottle (b) (4)

The Product Quality Review was conducted by the Quality Review Team, as shown in the **Table 2** below:

Table 2: Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Erin Skoda, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Muthukumar Ramaswamy, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Pei-I Chu, Ph.D.	OPF/DPAII/BranchVI
Microbiology	Pei-I Chu, Ph.D.	OPF/DPAII/BranchVI
Facility	Juandria Williams, Ph.D.	OPF/DIA/B3
Biopharmaceutics	Mei Ou, Ph.D.	ONDP/DB/BBII
Regulatory Business Process Manager	Thao, Vu	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Muthukumar Ramaswamy, Ph.D.	ONDP/DNDP-II/ Branch VI

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In his Quality Assessment Review, Swapan De, Ph.D, Application Technical Lead, concluded that, "regarding Chemistry Manufacturing and Controls, the application may be approved." He continued, "regarding quality aspects of the application and the drug substance, drug product, quality biopharmaceiutics, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application. The drug product has been granted a shelf life of 24 months under controlled room temperature storage conditions."

Site Inspections and Recommendations

Assessment of proposed manufacturing facilities was performed by Juandria Williams, Ph.D. The proposed sites and their proposed roles and responsibilities are listed in **Table 3** below (table constructed by this reviewer referencing Dr. Williams' review):

Table 3: Proposed Manufacturing and Testing Sites

Establishment Name	Location	FEI Number	Responsibilities
(b) (4)			
Dexcel, Ltd.	Or Akiva, Israel	3002806801	Testing (drug substance quality testing), packaging
Dexcel Pharma Technologies, Ltd.	Yokneam, Israel	3008404887	Manufacturing of lansoprazole DR ODT tablets

A pre-approval inspection (PAI) was conducted at the proposed testing site, Dexcel, Ltd., *Or Akiva, Israel*, in February 2016. For the other facilities, inspections were not deemed to be necessary, primarily based on the previous inspectional history of these facilities. Dr. Williams concluded that, "there appear to be no significant risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 208025."

Alcohol Dose Dumping

In the original NDA submission (12/05/2014), an in vitro alcohol-induced dose dumping study was conducted using 0.1 N HCl with 5%, 20%, and 40% (v/v) of alcohol. In this NDA resubmission, the in vitro alcohol-induced dose dumping study was repeated on the final drug product and the listed drug. Different levels of alcohol were added to the dissolution medium: 0%, 5%, 10%, 20%, and 40%. The (b) (4) tablets demonstrated similar dissolution behavior in comparison to the control (0% alcohol) and the dissolution specification of 10% drug release in the acid medium under all tested alcohol concentrations with the exception of the 40% alcohol medium, in which the Prevacid 24 HR (LD) product was also compromised. The in vitro alcohol dose dumping study demonstrated premature release of lansoprazole with alcohol at concentrations of ≥ 40%, ie, a shot of alcohol, but not a glass of wine or beer. These results indicate that in cases of higher alcohol concentrations the (b) (4) is compromised so the in vivo result will be premature release of drug in the stomach. Since lansoprazole is an acid-labile drug, an exposure of the drug to this gastric acid will lead to degradation of lansoprazole and result in ineffective drug. No greater drug exposure due to the compromised (b) (4) is expected. The sponsor has requested a waiver of the in vivo alcohol-induced dose dumping testing. The Office of Clinical Pharmacology (OCP) also evaluated the in vitro dose dumping study, and the Product Quality Team deferred evaluation of the acceptability of the proposed waiver to OCP. See **Section 5**, **Clinical Pharmacology**, for further discussion of this issue and for CDTL comments.

Environmental Assessment

The sponsor requested an exemption from submitting an Environmental Assessment. The Request was reviewed by Dr. Ramaswany and was granted because: 1) lansoprazole (Prevacid 24 HR, 15 mg capsules) is an approved drug. NDA approval action will not increase the use of the active moiety; and 2) once approved, use of lansoprazole DR ODT would not increase use of the active moiety in the environment as the product would be competing with the same market targeted by the approved drug. I agree.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology Review was conducted by Wafa Harrouk, PhD, DNDP. The sponsor did not conduct any new nonclinical studies to support approval of this NDA but is relying on the nonclinical safety data provided for the approval of the listed drug, Prevacid capsules (**NDA 20406**). All inactive ingredients used in manufacturing the primary tablets of lansoprazole DR ODT were within the allowable maximum potency as listed in the FDA Inactive Ingredients Database (IID). (b) (4) excipients, (b) (4) and the strawberry flavor, are not listed in the IID under these names; however, the individual subingredients are all listed in the IID. The sponsor provided individual letters of authorization for the DMFs for these excipients as well as qualitative and quantitative composition of the (b) (4) excipients' mixture, all of which were within acceptable limits in the IID list. The strawberry flavor is found in the IID under a different name. Stability testing resulted in the identification of three impurities (see **Section 3.0**, **Project Quality**), due to potential degradation, which were identified under accelerated conditions, all of which were within the ICH requirements for impurities/degradants. Dr. Harrouk recommended an approval action for this NDA.

Pregnancy and Lactation:

Lansoprazole is listed as Pregnancy Category B: reproduction studies have been performed in pregnant rats at oral doses up to 40 times the recommended human dose and in pregnant rabbits at oral doses up to 16 times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole. There are, however, no adequate or well-controlled studies in pregnant women. Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. The proposed Drug Facts Label (DFL) appropriately directs consumers that, "**If pregnant or breast-feeding**, ask a health professional before use," which is consistent with the language on the DFL for the listed drug, Prevacid 24HR.

5. Clinical Pharmacology

The Clinical Pharmacology Review was conducted by Sandhya Apparaju, Ph.D, Division of Clinical Pharmacology III, Office of Clinical Pharmacology. Dr. Apparaju concluded that the application is "acceptable from a Clinical Pharmacology perspective."

For this application, the sponsor conducted a bioequivalence study (**Project 120383**) to provide a scientific bridge to the safety and efficacy findings for the OTC listed drug, Prevacid 24 HR (lansoprazole, delayed-release 15 mg capsule; Novartis, **NDA 22327**), and a comparative food-effect bioavailability study (**Project 120384**).

Project 120383

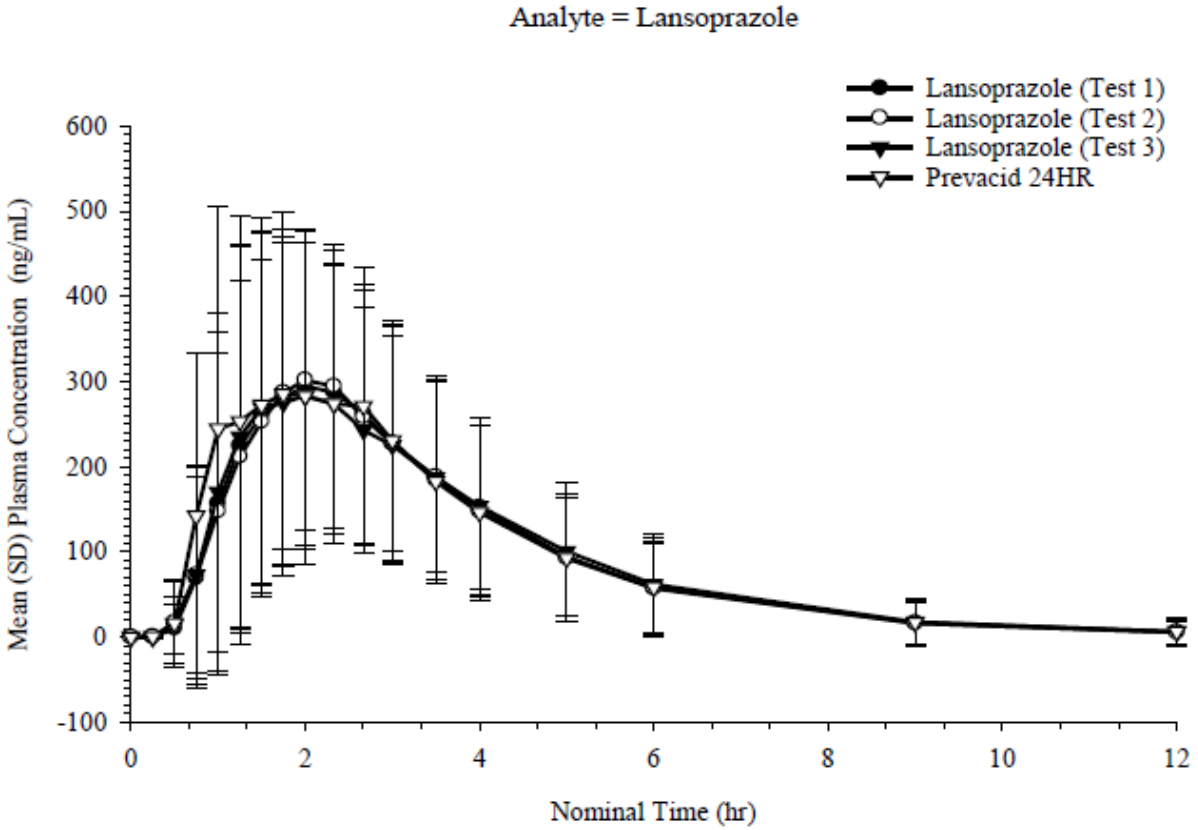
The bioequivalence (BE) study (**Project 120383**) was a single-center, randomized, single-dose, open-label, 4-way crossover study in 72 healthy male and female volunteers to compare the rate and extent of absorption of lansoprazole delayed-release ODT 15 mg given without and/or with water, or ODT swallowed intact with water compared to Prevacid 24 HR 15 mg delayed-release capsule under fasted conditions. The subjects received the following treatments, each separated by a 7-day washout period:

- 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 24 HR) swallowed with water.

Subjects were randomized (1:1:1:1) into one of the following sequence groups: ABDC, BACD, CBDA, or DCAB. Blood samples for pharmacokinetic analysis were collected prior to study drug administration and 0.25, 0.5, 0.75, 1.0, 1.25, 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 time period. Pharmacokinetic parameters assessed included AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $t_{1/2}$, and K_{el} (elimination rate constant). Sixty subjects completed all treatment periods.

Mean concentration versus time profiles by treatment are presented are presented in **Figure 2** below. The mean profiles for both treatments are plotted based on the mean plasma concentration levels calculated per timepoint.

Figure 2: Mean Concentration-time Profile for Lansoprazole for Each Treatment: Project 120383



Source: CSR Project 120383, Figure 11.4.2.3-1, page 37.

Pharmacokinetic parameters generated by the sponsor using non-compartmental analyses of the lansoprazole plasma concentration-time data are summarized in **Table 4** below. Note that Subject 43 was withdrawn from the study due to difficulty with blood collection, and Subject 72 elected to withdraw from Period 1 due to personal reasons and came back for Period 3 and 4. Subject 65 elected to withdraw from Period 1 due to personal reasons and came back for Period 4. Subjects 2, 5, 8, 9, and 14 withdrew due to personal reasons ,and Subject 67 withdrew due to insuitable vein assessment. Two subjects (Subject 47, elective abortion; and Subject 2, withdrawn from Period 2 due to post-procedural discomfort and dizziness, however returned for Periods 3 and 4) were withdrawn due to adverse events. Subject 7 was withdrawn from statistical analysis of comparison C/D as the dosing procedure was not repeated

for Test 3 (Treatment C): subjects must complete at least two periods (1 test and 1 reference) with adequate characterization of PK profile in order for data inclusion for PK and statistical analyses.

Table 4: Summary of Pharmacokinetic Parameters for Lansoprazole for Each Treatment: Project 120383

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

[a] Median
(Min - Max)

[1] Profile of Subjects 43and 72 was excluded
[2] Profile of Subjects 8, 43, 47 and 71 was excluded
[3] Profile of Subjects 2, 7, 9, 27, 43, 47, 65 and 67 was excluded
[4] Profile of Subjects 43 was excluded

Source: CSR Project 120383, Table 11.4.2.3-1

Dr. Apparaju conducted a BE analysis using SAS 9.3, which is shown in **Table 5** below (electronically copied and reproduces from Dr. Apparaju's review):

Table 5: Results of Average BE Analysis: Project 120383

	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; Prevacid 24 HR
Electronically sopied and reproduced from Dr. Apparaju's review.

As shown in **Table 5**, with the exception of the C_{max} for Treatment B, all of the 90% confidence bounds for the test/reference least squares mean (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 C_{max} was slightly below the regulatory threshold of 80%. However, the AUCs were within BE ranges for all treatments. Dr. Apparaju concluded that, " the observed modest decrease (relative to reference D) in C_{max} for treatment B is unlikely to have any clinical implications, especially given that the AUC parameters were bioequivalent. Furthermore, Dr. Apparaju concluded 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 Prevacid 24 HR delayed release OTC capsule.

<u>CDTL Comment</u>: I agree with Dr. Apparaju's assessment amd conclusions. Bioequivalence to the listed drug was adequately demonstrated in this study. For Treatment B, I agree that lower 90% confidence bound for C_{max} being below the regulatory thereshold of 80% is unlikely to have clinical implications, because the lower confidence bound was only slightly low (~79%) and all AUC parameters were bioequivalent.

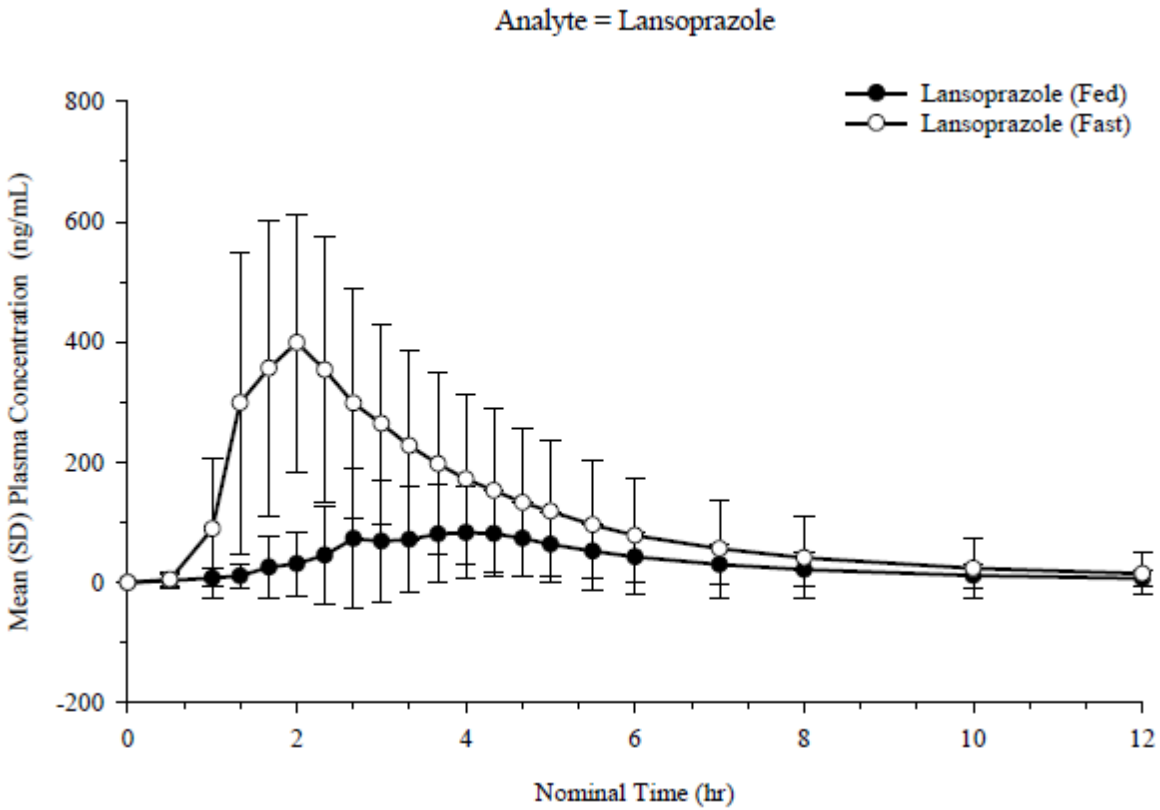
Project 120384

The food effect study (**Project 120384**) was a single-center, randomized, single-dose, open-label, 2-way crossover, comparative bioavailability study to compare the rate and extent of absorption of lansoprazole delayed-release orally disintegrating tablet 15 mg administered as one dose under fed and fasted conditions. A total of 18 healthy, adult subjects were randomized and dosed in this study; 17 subjects completed both study periods. One subject withdrew in Period 2 due to symptoms of severe headache and hot flush prior to dosing. For the "fed treatment" (Treatment A), after a supervised overnight fast of at least 10 hours, subjects received a high-fat, high-caloric breakfast 30 minutes before drug administration. For the fasted treatment (Treatment B), subjects were required to fast for at least 10 hours before dosing. For both treatment periods, subjects were required to place the ODT tablet on their tongue until it disintegrates completely and then swallow it. No water was allowed. All subjects were required to fast for 4 hours after dosing. There was a washout period of at least 3 days between treatments.

In each Treatment Period, blood samples were drawn for PK analyses prior to drug administration and at 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. Pharmacokinetic parameters assessed included AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $t_{1/2}$, and K_{el}

Mean plasma lansoprazole concentration-time curves for the fed and fasted groups are shown in **Figure 3** below:

Figure 3: Mean Concentration-time Profile for Lansoprazole for Each Treatment (n=17): Project 120384)



Source: CSR vProject 120384, Figure 11.4.2.3-1

Mean plasma lansoprazole pharmacokinetic parameters are summarized in the **Table 6** below:

Table 6: Summary of Pharmacokinetic Parameters for Lansoprazole for Each Treatment: Project 120384)

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

Source CSR Project 120384, Table 11.4.2.3-1, p33

Based on the sponsor's data, Dr. Apparaju calculated an average bioequivalence analysis using Pharsight Phoenix and provided the following results, which are comparable to the sponsor's data:

Table 7: Results of Average Bioequivalence Analysis: Project 120384

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]

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Dr. Apparaju concluded that, "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. I agree with Dr. Apparaju's assessment.

Alcohol Dose Dumping

Dr. Apparaju also evaluated the in vitro dose-dumping study (see **Section 3: Product Quality**). Dr. Apparaju concluded, "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.

CDTL Comments: Regarding alcohol dose dumping, I agree with the assessment of Dr. Apparaju. The acid-labile lansoprazole will be degraded upon early release, so there is no safety concern. The only concern is that the dose will not be efficacious. Under Directions, the proposed Drug Facts Label (DFL) states, "do not take this medicine with alcohol." Even is a consumer took the product with a glass of beer or wine, efficacy would likely not be effected. Efficacy would only be hindered with an alcohol concentration of 40%, equivalent to a shot of alcohol. If someone took a shot of alcohol with this medication every day for 14 days, he or she would likely no achieve relief of heartburn and should in any case see a physician. The proposed DFL advises to Stop use and ask a doctor if "you need to take this product for more than 14 days."

Dr. Apparaju also provided the following 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 states 'do not take this medicine with alcohol'. This is acceptable due potential for loss of efficacy with alcohol, particularly at higher alcohol strength.

It should be noted that, OCP initially recommended the following labeling changes, which were written in Apparaju's review:

- 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

However, in an Addendum to OCP Review of NDA 208025 (5/16/16), Dr. Apparaju wrote:

> *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".*

CDTL Comments: I agree that the labeling language, "take (b) (4) *before eating" is acceptable because it is consistent with the Prevacid labels and, as Dr. Apparaju noted, the dose in the clinical trials which demonstrated efficacy was administered "before eating" or "before breakfast" without specifying a period of time before eating.*

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No efficacy trials were conducted in support of this application. The sponsor intends to rely on FDA efficacy and safety findings 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 approval of this application. The sponsor has conducted a bioequivalence study (Project **120383**), which is described in **Section 5** above, to provide the scientific bridge to FDA findings of efficacy for Prevacid 24 HR.

The efficacy of the LD, Prevacid 24HR, for the treatment of frequent heartburn was demonstrated in 1,986 adults in the two double-blind, randomized, controlled trials conducted for the approval of Prevacid 24HR, which were identified in the literature (Kushner, 2009; Peura, 2009). Efficacy was defined in these two studies by analysis of the percentage of nighttime with no heartburn and the percentage of 24-hour days with no heartburn in comparison to placebo. Treatment with Prevacid 24HR demonstrated a significantly

higher mean percentage of 24-hour days with no heartburn and a significantly higher mean percentage of nighttime with no heartburn in both trials (Kushner, 2009; Peura, 2009).

8. Safety

The safety database provided by the sponsor was adequate for review. The sponsor did not conduct any clinical safety studies in support of this application. The safety database relied on the following, which were extensively reviewed by Dr. Parikh:

- Safety data obtained from the bioequivalence study (**120383**) and the food-effect study (**120384**)
- FDA findings of safety for Prevacid 24HR (**NDA 22327**, Novartis)
- Published literature
- Postmarketing databases (2008 to present):
    - FDA Adverse Events Reporting System (FAERS)
    - DAWN
    - National Poison Data System (NPDS)
    - World Health Organization (WHO)

An Integrated Summary of Safety (ISS) was submitted with the NDA for the cumulative time period of 2008 to 2014, and a 120-day Safety Update was submitted for the time period up to September 15, 2015.

Overall Extent of Exposure

A total of 90 subjects were exposed to the proposed OTC Lansoprazole Delayed-Release ODT product (72 subjects in **Project 120383**; 18 subjects in **Project 120384**), with single day dosing regimens of 15 mg lansoprazole under fed and fasted conditions and administration with and without water. The sponsor also relied on the safety data of lansoprazole in 3 pivotal clinical studies (1138 patients) identified in the published literature (see **Section 7**) that were conducted to support the approval of the LD, Prevacid 24 HR (**NDA 22327**). In addition, the approved Prevacid (lansoprazole delayed release capsule, 15 mg. 30 mg, **NDA 20406**) labeling states that over 10,000 patients have been treated with Prevacid in Phase 2 or 3 clinical trials involving various doses and durations of treatment (Takeda Pharmaceuticals America, 2014). The sponsor has provided literature references to these studies for supportive safety data.

Sponsor's Pharmacokinetic Studies

In the two studies (**Project 120383** and **Project 120384**) conducted by the sponsor, there were no deaths or serious adverse events (SAEs) reported. There were no clinically significant changes in clinical laboratory findings, vital signs, or electrocardiograms. Twelve subjects were discontinued from the study: however, three out of eight subjects who withdrew for personal reasons returned to participate in the later stages of the PK studies. Three subjects withdrew due to adverse events and are listed in the **Table 8** below.

Table 8: Dropouts due to Adverse events by Treatment Arm (Project 120383 and Project 120384)

Adverse Event Dropout Listing (Combined Safety Population)

Trial	Center	Subject	Age	Sex	Treatment	Dose (mg)	Time (days)	Body System	Preferred term	Adverse Event	Serious ?	Outcome
120383	iHC	120383-27	18	Male	D	15	6	Injury, poisoning and procedural complications	Post procedural discomfort	Hot flashes following catheter insertion	No	Spontaneous
120383	iHC	120383-27	18	Male	D	15	6	Nervous system disorders	Dizziness	Dizziness	No	Spontaneous
120383	iHC	120383-47	35	Female	D	15	0	Pregnancy, puerperium and perinatal conditions	Abortion	Abortion	No	With treatment
120384	iHC	120384-07	39	Female	A	15	6	Nervous system disorders	Headache	Headache	No	With Treatment
120384	iHC	120384-07	39	Female	A	15	6	Vascular disorders	Hot flush	Hot flashes	No	Spontaneous

Center: iHC = InVentiv Health Clinique

Time (days) is calculated as the number of days between adverse event onset and the previous study medication administration.

Treatment A = Dexcel Pharma Technologies Ltd., Israel, lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, allowed to disintegrate and swallowed without water (fasting conditions).

Treatment B = Dexcel Pharma Technologies Ltd., Israel, , lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, allowed to disintegrate and swallowed with water (fasting conditions).

Treatment C = Dexcel Pharma Technologies Ltd., Israel, lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, swallowed with water (fasting conditions).

Treatment D = Novartis, U.S.A (Prevacid® 24HR), lansoprazole 1 x 15 mg delayed-release capsule, swallowed with water (fasting conditions).

Treatment E = Dexcel Pharma Technologies Ltd., Israel, lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, allowed to disintegrate and swallowed without water (fed conditions).

Brief narrative summaries of the three subjects who withdrew due to adverse events are as follows:

- Subject 27 withdrew due to dizziness and post-procedural discomfort after blood draw.

- Subject 7 experienced the significant TEAEs "Headache" and "Hot flush" approximately 5 hours and 1 hour, respectively, prior to study drug administration in Period 2, and was withdrawn from the study as a precautionary measure. The subject was put in recline position and her vital signs were carefully monitored until resolution. The TEAE "Headache" resolved with treatment approximately 10 hours after the onset and TEAE "Hot flush" resolved spontaneously 45 minutes after the onset. Both of these TEAEs were judged mild in severity and were considered to be unrelated to the study medication.

- Subject 47 experienced the significant AE "Abortion" approximately 25 days following lansoprazole administration in Period 2 (Treatment D). Her last menses started on February 05, 2014 (onset of pregnancy). The urine pregnancy test performed at screening and the serum pregnancy test performed prior to study drug administration in Periods 1 and 2 yielded negative results. However, the serum pregnancy tests performed prior to dose administration in Period 3 (Human chorionic gonadotropin [β-HCG] of 182.5 IU/L) yielded positive results. The subject was withdrawn prior to study drug administration in Period 3. The subject voluntarily terminated her pregnancy.

*CDTL Comment: It is extremely unlikely that the adverse events resulting in discontinuation from the study were related to study drug. For Subject 27, it appears that the AEs were related to phlebotomy, and for Subject 47, the voluntary abortion clearly was not related to study drug. For Subject 7, headache and hot flush might be reasonably attributed to study medication: however, the AEs occurred 5 hours and 1 hour, respectively, prior to study drug administration in Period 2. Since the washout period was 7 days, and since the study in which she was participating demonstrated that the half-life for the study drug was ~2.2 hours in fed state and ~1.3 hours in fasting state (see **Section 5**), no study drug would have been present in Subject 7 at the time of the AEs; therefore, the AEs were unrelated to study drug.*

A total of 62 treatment emergent adverse events (TEAEs) were reported. Most were mild, and only 35 of these adverse evetns (AEs) were considered to be related to lansoprazole. As shown in the **Table 9** below, headache was the most frequently reported TEAE, which was reported in 17 subjects. Importantly, AEs were similar across all treatment groups, and specifically there was no difference in AEs observed for the proposed ODT tablets and the LD (Treatment D) (0.82; CI 95% (0.235-2.911). In addition, no difference in the number of AEs or their severity was observed when comparing Treatment A (tablets were allowed to disintegrate and were then swallowed) to Treatment C (tablets were swallowed whole) (0.65; CI 95% (0.192-2.223).

Table 9: Incidence of Commonly Occurring TEAEs (>1 Subject of the Combined Overall Safety Population [Project 120383 and Project 120384])

System Organ Class MedDRA® Preferred Term	Treatment Group				
Number of subjects dosed	A 87	B 69	C 64	D 69	E 17
Gastrointestinal disorders					
Nausea	1 (1.1%)	1 (1.4%)	1 (1.6%)	3 (4.3%)	
Stomatitis		2 (2.9%)	1 (1.6%)		
Tongue disorder	1 (1.1%)	1 (1.4%)		1 (1.4%)	
General disorders and administration site conditions					
Asthenia		1 (1.4%)		1 (1.4%)	
Injury, poisoning and procedural complications					
Post procedural discomfort	2 (2.3%)			1 (1.4%)	
Procedural dizziness	1 (1.1%)			1 (1.4%)	
Nervous system disorders					
Dizziness		1 (1.4%)	2 (3.1%)	1 (1.4%)	
Headache	6 (6.9%)		6 (9.4%)	5 (7.2%)	
Somnolence	1 (1.1%)	2 (2.9%)	1 (1.6%)	2 (2.9%)	
Respiratory, thoracic and mediastinal disorders					
Nasal congestion	1 (1.1%)	1 (1.4%)	1 (1.6%)		
Vascular disorders					
Hot flush	2 (2.3%)				

MedDRA®: Medical Dictionary for Regulatory Activities.

Treatment A = Dexcel Pharma Technologies Ltd., Israel, lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, allowed to disintegrate and swallowed without water (fasting conditions).

Treatment B = Dexcel Pharma Technologies Ltd., Israel, , lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, allowed to disintegrate and swallowed with water (fasting conditions).

Treatment C = Dexcel Pharma Technologies Ltd., Israel, lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, swallowed with water (fasting conditions).

Treatment D = Novartis, U.S.A (Prevacid® 24HR), lansoprazole 1 x 15 mg delayed-release capsule, swallowed with water (fasting conditions).

Treatment E = Dexcel Pharma Technologies Ltd., Israel, lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, allowed to disintegrate and swallowed without water (fed conditions).

Source: ISS; Table 2, page 10

Studies Conducted for the Approval of Prevacid 24HR

As stated above, in addition to supportive safety data obtained from the literature on Prevacid the sponsor (lansoprazole delayed release capsule, 15 mg. 30 mg, **NDA 20406**), the sponsor relied on safety data from 3 clinical trials (1138 patients) identified in the published literature that were conducted to support the approval of the listed drug, Prevacid 24 HR (**NDA 22327**). All 3 of the trials were efficacy and safety studies for the treatment of frequent heartburn in adults age 18 and older over 14 days. Summary exposure of lansoprazole in the 3 trials is listed in the **Table 10** below (the Kushner reference includes the results of 2 studies):

Table 10: Summary of Exposure Reported in the Published Literature

Source	Drug(s), Dose, Route	Duration of Treatment	Number of Subjects
RELY			
(Peura, 2009) Treatment of frequent heartburn	Lansoprazole, oral 15 mg daily 30 mg daily	14 days	291 277
(Kushner, 2009)[a] Treatment of frequent heartburn	Lansoprazole, 15 mg, oral	14 days	570

Source: ISS; Table 2, page 10

For these three studies (Kushner, 2009; Peura, 2009), the adverse events were similar in frequency and severity to what was observed in the pharmacokinetic studies conducted by the sponsor. The AEs were mostly of mild or moderate intensity, transient, and similar across treatment groups. As shown in the **Table 11** below, in one of the studies (Peura, 2009), the incidence of AEs suspected to be related to the study medications did not differ between the active treatments (15 mg and 30 mg) and placebo, although more subjects experienced drug-related AEs in the 30 mg group (14), than the 15 mg group (3), or placebo (7). All SAEs were determined to be unrelated to the study treatment. The most common AEs reported were gastrointestinal disorders and nervous system disorders.

Table 11: Adverse Events from Prevacid 24HR (Peura, 2009)

Adverse Event	Placebo (N=284), n(%)	15 mg once daily (N=291), n(%)	30mg once daily (N=277), n(%)
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The adverse events reported in the two other clinical studies submitted for the approval of the LD, Prevacid 24HR (Kushner, 2009), were also similar to the events reported for the sponosr's pharmacokinetic studies. Overall, the events were considered mild and were similar across treatment groups. Only 5 subjects treated with lansoprazole experienced AEs that were related to lansoprazole, as shown in the **Table 12** below:

Table 12: Common Adverse Events from Prevacid 24 HR Pivotal Studies (Kushner, 2009)

Adverse Event	Study 1		Study 2	
	Lansoprazole 15 mg (N = 282), n (%)	Placebo (N = 282), n (%)	Lansoprazole 15 mg (N = 282), n (%)	Placebo (N = 282), n (%)
COPYRIGHT MATERIAL WITHHELD				

Electronically copied and reproduced from sponsor's submission; ISS, Table 9, page 28 [Source: Kushner, 2009]

Adverse Events for the Prevacid (NDA 20406, Prescription Dose)

The most commonly reported adverse reactions (≥ 1%) in the approved labeling for Prevacid were: diarrhea, abdominal pain, nausea, and constipation (Takeda Pharmaceuticals America, 2014). Section 6.1 of Prevacid Prescribing Information states, "worldwide, over 10,000 people have been treated with Prevacid in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. In general, Prevacid treatment has been well-tolerated in both short-term and long-term trials." Section 6.1 also includes the

following table of "adverse reactions….reported by the treating physician to have a possible or probable relationship to drug in 1% or more of Prevacid-treated patients and occurred at a greater rate in Prevacid-treated patients than placebo-treated patients."

Table 13: Incidence of Possibly or Probably Treatment-Related Adverse Reactions in Short-Term, Placebo-Controlled Prevacid Studies

Body System/Adverse Event	Prevacid (n = 2768) %	Placebo (n = 1023) %
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Section 6.1 continues, "Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received 15 mg and 30 mg of Prevacid, but higher in the patients who received 60 mg of Prevacid (2.9%, 1.4%, 4.2%, and 7.4%, respectively). The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

Oropharyngeal Assessments

Due to the orally disintegrating drug delivery technology, the sponsor was required to conduct oropharyngeal assessments in the pharmacokinetic studies. Oropharyngeal assessments were conducted by certified physicians and nurses, and severity level was determined based on the following table (electronically copied and reproduced from Dr. Parikh's review):

Table 14: Oropharyngeal Assessment Severity Scale

Severity classification	Description of symptoms
Mild	Minor erythema or irritation signs at the application site only
Moderate	erythema or irritation signs beyond the application site with or without edema
Severe	erythema or irritation signs with or without edema with presence of ulcers, vesicles or bullae

[Source: Sponsor's electronic submission, Section 5.3.5.3 page 11/114]

In **Project 120383**, 90 subjects participated in the evaluation. The analysis covers 308 periods of single dose exposure. Oropharyngeal findings were found in 14 out of the 308 periods evaluated: 11 findings described in 6 subjects were considered not related since they were also present before dosing. Three findings (light redness on tongue) were considered possibly related and were noted in Subject 18 (received Prevacid 24 HR) and in Subjects 36 and 33 (received the ODT). The light redness was also noticed in Subject 36 in previous exposure period before dosing. In all three cases the redness was classified as mild and spontaneously resolved. No oropharyngeal findings were found when the patients were discharged.

Table 15: Summary of Oropharyngeal Assessments

	Number of subjects	**Number of periods of single dose evaluation**	**Number of findings**	
			Unrelated	**Possibly related**
Study 120383	72	273	11	3
Study 120384	18	35	0	0
Total	90	308	11	3

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No oropharyngeal findings were observed in **Project 120384**.

The sponsor concluded that the oropharyngeal observations made during the conduct of the studies, suggest the proposed product can be safely administered to the general population. I agree with the sponsor's assessment.

Postmarketing Data

Overall, the safety narrative from the postmarketing safety databases and published literature is consistent with the known safety profile of lansoprazole. Most of the adverse events that are applicable for the sponsor's OTC lansoprazole drug product are infrequent and minor. Many of the safety signals identified are related to higher doses of lansoprazole and longer dosing durations than the sponsor's proposed product. The 4 postmarketing databases that were analzyed were FAERS, DAWN, NPDS, and WHO. All databases were searched back to 2008 through the most recently available data.

National Poison Data System (NPDS:)

Between 2008 and 2015 (including 120-day Safety Update), the total number of events were 13,066. The database is unable to distinguish marketing status (Rx versus OTC). In general, children under the age of 10 were involved in the highest number of poisoning events (8884); this number was more than 10 times the next most frequently reported age group of 10 to 19 (772). The sponsor will not be marketing the proposed drug product to the pediatric population. In addition, the sponsor will be packaging the proposed drug product in (b) (4) containers, which will reduce the risk of poisoning events. The NPDS data suggests fewer poisoning events with shorter duration of use as proposed by the sponsor.

FDA Adverse Events Reporting System (FAERS):

A total of 3,528 events were reported in 1,006 subjects during the period 2008 to second quarter of 2015. The majority of the AEs were associated with higher dosing and longer duration of lansoprazole Rx product than proposed for the lansoprazole OTC drug product. The LD, Prevacid 24HR (**NDA 022327**) was listed only nine times in the FAERS database during the timeframe examined

(2008 to second quarter 2015). There was no increase in AEs in the ODT formulation compared to the capsule formulation. The most common AEs in the FAERS database are abdominal pain, diarrhea, and nausea. This is in line with prescribing information of Prevacid Rx. Other frequently reported AEs included dizziness, confusion state, rash, pruritis, and metabolic disorders including hypomagnesemia, hyponatremia, and hypocalcemia. The lack of AEs pertaining to the oral cavity which included safety data from both dosage forms of Prevacid 24HR capsules (**NDA 022327**, Novartis) and Prevacid SoluTab (**NDA 021428**, Takeda) suggests that there is no increased risk for any specific AEs for the ODT product. Furthermore, the majority of the AEs that were reported were associated with lansoprazole treatment duration of >14 days which may be lower with the proposed product since the sponsor is requesting approval for a 14-day course.

World Health Organization (WHO):

A search of the WHO publications database revealed a list of publications which present several known safety issues associated with lansoprazole and PPIs in general. The majority of the reports were already evaluated by FDA and led to a class labeling change in PPIs. Only *Clostridium difficile*-Associated Diarrhea (CDAD) and drug-drug interactions with Atazanavir, methotrexate, and mycophenolate mofetil are relevant for the proposed drug product. The rest of the adverse reactions such as hypomagnesemia, bone fractures, interstitial nephritis are associated with PPIs intended for long-term treatment, and drug interaction with clopidogrel is associated with omeprazole and esomeprazole only.

Drug Abuse Warning Network (DAWN):

The sponsor evaluated the DAWN database from 2004 to 2011. The database evaluates PPIs as a class and does not identify specific PPIs. Over this time period, weighted annual estimates of emergency department visits ranged from a low of 2,149 in 2005 to a high of 8,879 in 2010. The majority of abuse and misuse cases occurred with users age 35 and older. Overall, the majority of patients were treated and released to their homes. Most poisoning events and misuse and abuse events were considered to have little or no toxic effect.

Literature Review:

The sponsor conducted a PubMed query and identified 30 studies. Most of the studies used a higher dose of lansoprazole for a longer duration than in the OTC setting. The reported AEs were in line with the AEs reported in the prescribing information of lansoprazole prescription product. Overall, the AEs reported in the literature for lansoprazole were mild in nature and the most common reported AEs were abdominal pain and headache.

Safety Conclusions

In his review, Dr. Parikh concluded that, "no new safety concerns were identified regarding the safety of lansoprazole ODT for OTC use. The safety profile of the proposed product is expected to be comparable to that of the currently marketed Prevacid 24HR OTC product." I agree with Dr. Parikh's assessment. In the two pharmacokinetic studies, there were no unexpected or serious safety findings, and the sponsor's search of safety databases (NPDS, FAERS, WHO, and DAWN) and published literature did not identify any new safety signals of concern which necessitate changing to OTC labeling. Drug interactions of concern (warfarin, prescription antifungal or anti-yeast medicines, digoxin, theophylline, tacrolimus or mycophenolate mofetil, atazanavir, and methotrexate) are already listed in the "Ask a doctor ot pharmacist before use" section. (b) (4)

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The sponsor is requesting a full waiver for all pediatric populations. An Initial Pediatric Study Plan (iPSP) dated February 28, 2014 was submitted to Pre-Investigational New Drug application 118528. The sponsor submitted an agreed iPSP requesting a full waiver for pediatric studies for the OTC treatment of heartburn and to exclude the use of lansoprazole ODT in the pediatric population (all ages of 0 to <18) on July 1, 2014. The Agency received the agreed iPSP on July 3, 2014. The sponsor received approval on December 16, 2014 for lansoprazole ODT and was granted full pediatric waiver.

I concur with the request for a waiver of pediatric studies. FDA has waived pediatric studies for the other PPIs because, as stated by Dr. Leonard-Segal in her Summary Review of OTC lansoprazole (**NDA 22327**; May 11, 2009), "it would not be safe to use this medication OTC in the pediatric population since the underlying causes for heartburn in children should be evaluated by a healthcare professional."

The proposed labeling states under Directions, " adults 18 years of age and older." However, the listed drug (Prevacid 24 HR) Directions state "children under 18 years of age: ask a doctor *before use*" (italics added by reviewer). The proposed DFL should be aligned with the LD DFL (see **Section 12**).

11. Other Relevant Regulatory Issues

As noted in Dr. Parikh's review, the sponsor attested that the study was conducted in compliance with the protocol, GCP, GLP, and all applicable regulations, including the FDA Cosmetic Act, CFR 21, and any Independent Ethics Committee (IEC) requirements relative to clinical studies and the recommendations laid down in the most recent version of the Declaration of Helsinki. The sponsor submitted the FDA Form 3454 certifying that it has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator(s) could be affected by the outcome of the study.

12. Labeling

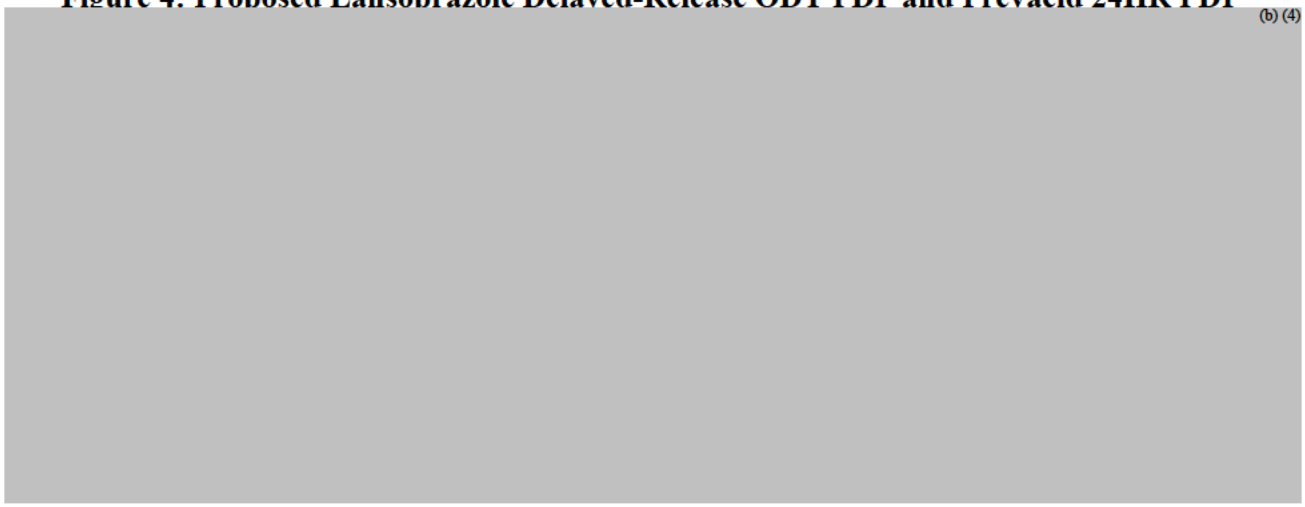
The sponsor's proposed Drug Facts Label (DFL) is as follows (electronically copied from Dr. Jones' review:

Table 16: Sponsor's Proposed DFL for Lansoprazole Delayed-Release Orally Disintegrating Tablets (submitted on August 6,

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed carton labeling. The sponsor did not submit a proprietary name for this proposed product; however, the sponsor indicated that a request for proprietary name review will be submitted once a reviewer is identified. The primary reviewer, Grace P. Jones, PharmD, BCPS, noted that the proposed carton labeling contains (b) (4) the tablet on the principal display panel (PDP). Although

incorporation of the image of the product follows [redacted] (b) (4) is different, as shown in **Figure 4** below (electronically sopied and reproduced from Dr. Jones' review.

Figure 4: Proposed Lansoprazole Delayed-Release ODT PDP and Prevacid 24HR PDP



Dr. Jones concluded that [redacted] (b) (4) the tablet image which contains the imprint "15" (denoting tablet strength) [redacted] (b) (4) should be relocated. Furthermore, Dr. Jones noted that the statement "May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours" is located on the PDP of the proposed Lansoprazole delayed-release orally disintegrating tablets, [redacted] (b) (4). Furthermore, the image of the tablet in the carton labeling should reflect the actual representation of the true size, color, and imprint of the tablet. I agree with Dr. Jones recommendations.

Labeling review was conducted by Mary Vienna, RN, MHA, DNDP, ODE IV. In her review, she agreed with Dr. Jones' recommendations above and provided several additional labeling recommendations. Some of her recommendations relate to formatting and font issues. In addition to Dr. Jones' recommendations, her major recommendations are as follows:

1. As currently proposed, the other text competes with the established name for consumers' attention on the PDP and may be confusing. Therefore, Ms Vienna recommended to increase the relative prominence of the established name, lansoprazole.

2. The RLD directions on how to take the drug are contained in the fourth bullet "[bullet] Swallow whole. Do not crush or chew tablets." The proposed labeling moves the "Swallow whole" instruction to the (b) (4)
3. The last bullet in the Directions section states (b) (4)
4. The sponsor provided a 7-count blister label. FDA has expressed concern that a 7-count, which is not approved for the listed drug or any other OTC PPI, could result in consumers determining that the product is efficacious by day 7 and discontinue their treatment. Ms. Vienna recommends that the sponsor provide data to demonstrate that consumers understand labeled instructions that two packaged bottles or blisters represent a full course of treatment.

In his review, Dr. Parikh recommended the phrase pertaining to subsection "14-Day Course of Treatment" under "Directions" sections which states, "do not chew or crush tablets" should be bolded and combined with the first bullet or as a separate bullet in the second position due to the potential for reduced efficacy if a consumer fails to follow these important instructions as explained above.

CDTL Comments: In general, the proposed labeling changes proposed by OCP, DMEPA, Labeling Team, and Clinical are appropriate. The exact wording of any labeling changes to be requested by the sponsor will be determined in internal labeling meetings which are ongoing at the time of this review.

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

I recommend approval action for this application. The approval is contingent upon satisfactory labeling negotiations with the sponsor. See Benefit-Risk Summary and Assessment.

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

/s/

FRANCIS E BECKER
05/21/2016