

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208025Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	2016 06 07
<b>From</b>	Karen Murry Mahoney, MD, FACE Deputy Director, Division of Nonprescription Drug Products Office of Drug Evaluation IV Office of New Drugs Center for Drug Evaluation Research
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA/BLA #</b>	NDA 208025
<b>Supplement #</b>	(b) (4)
<b>Applicant Name</b>	Dexcel Pharma Technologies
<b>Date of Submission</b>	2014 12 05 (original submission, but had Refusal to File deficiencies) 2015 08 07 (resubmission)
<b>PDUFA Goal Date</b>	2016 06 07
<b>Proprietary Name / Established (USAN) Name</b>	No proprietary name submitted. Established name lansoprazole
<b>Dosage Forms / Strength</b>	Delayed-release orally disintegrating tablet, 15 mg
<b>Proposed Indication(s)</b>	Drug Facts label Use statement: treats frequent heartburn (occurs 2 or more days a week)
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted OND Action Package, including:</b>	<b>Names of Discipline Reviewers</b>
Medical Officer Review	Ketan Parikh, MD
Pharmacology Toxicology Review	Wafa Harrouk, PhD
Quality Review: Drug Substance	Erin Skoda, PhD
Quality Review: Drug Product	Muthukumar Ramaswamy, PhD
Quality Review: Process	Pei-I Chu, PhD
Quality Review: Microbiology	Pei-I Chu, PhD
Quality Review: Facility	Juandria Williams, PhD
Quality Review: Biopharmaceutics	Mei Ou, PhD
Quality Review: Regulatory Business Process Management	Vu Thao
Quality Review: Application Technical Lead	Swapan K. De, PhD
Quality Review: Environmental Assessment	Muthukumar Ramaswamy, PhD
Microbiology Review	
Clinical Pharmacology Review	Sandhya Apparaju, PhD
CDTL Review	Francis Becker, MD
OSE/DMEPA	Grace P. Jones, PharmD, BCPS
Division of Nonprescription Drug Products Interdisciplinary Scientist Labeling Review	CPT Mary R. Vienna, RN, MHA
Division of New Drug Bioequivalence Evaluation, Office of Study Integrity and Surveillance	Shila S. Nkah

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

CDTL=Cross-Discipline Team Leader

## 1. Introduction

Dexcel Pharma Technologies (hereafter referred to as Dexcel) has submitted a 505(b)2 application for a new dosage form (an orally disintegrating tablet) of lansoprazole, a proton pump inhibitor indicated for nonprescription treatment of frequent heartburn in patients 18 years of age and older.

All review disciplines recommend approval, and I concur.

In this decisional memorandum, I will address a few areas of regulatory interest, including:

- the bioequivalence data supporting the application
- the effect of food on the pharmacokinetics of the drug
- oral safety
- a proposed 7-dose blister card presentation

None of these issues affect approvability.

## 2. Background

Proton pump inhibitors (PPIs) reduce gastric acid secretion by inhibition of the hydrogen/potassium adenosine triphosphate enzyme system, also referred to as the proton pump. The proton pump is the terminal step in gastric acid production, and is responsible for secretion of H<sup>+</sup> ions into the stomach. The reduction of acid in the stomach achieved by PPIs aids in prevention and healing of certain ulcers, treatment of gastroesophageal reflux disease, and relief of the symptoms of heartburn. Lansoprazole is one of several approved PPIs.

The first lansoprazole product, prescription Prevacid®, was approved in 1995. Its current indications (abbreviated) are:

- Short-term treatment of active duodenal ulcer
- *Helicobacter pylori* eradication in patients with duodenal ulcer disease (in conjunction with antibiotic therapy)
- Maintenance of healed duodenal ulcers
- Short-term treatment of active benign gastric ulcer
- Healing of gastric ulcer associated with treatment with nonsteroidal anti-inflammatory drugs
- Maintenance of healing of erosive esophagitis
- Pathological hypersecretory conditions including Zollinger-Ellison syndrome

Prevacid 24 HR (NDA 22327), a nonprescription lansoprazole 15 mg delayed-release capsule, was approved in 2009, for use for frequent heartburn.

On December 5, 2014, Dexcel submitted a 505(b)(2) application for an orally disintegrating tablet dosage form of lansoprazole. However, on February 6, 2015, FDA issued a Refusal to File letter. Please refer to that letter for full details of the deficiencies. In brief:

- The application did not include an integrated summary of safety, adequate safety datasets for the pivotal pharmacokinetic studies, details on coding and adjudication of adverse event terms, adequate data regarding oropharyngeal safety assessments, adequate postmarketing safety data, and safety information to support use throughout a 14-day course of treatment.
- The application was not in the required format with regard to summary and analysis of postmarketing safety data and literature references.

Dexcel addressed those deficiencies and resubmitted its NDA on August 7, 2015.

Dexcel is relying in part upon FDA's finding of safety and efficacy for Prevacid 24 HR (NDA 22327, nonprescription lansoprazole delayed-release capsule, 15 mg) to support approval of this proposed lansoprazole orally disintegrating tablet (NDA 208025), via the 505(b)(2) regulatory pathway. In order to provide a scientific bridge between NDA 22327 and Dexcel's lansoprazole orally disintegrating tablet (ODT), Dexcel conducted a bioequivalence study and a food effect study.

### **3. CMC/Device**

I concur with the conclusions reached by Dr. Swapan De and the quality review team members regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

### **4. Nonclinical Pharmacology/Toxicology**

I concur with the conclusions reached by Dr. Wafa Harrouk, the pharmacology/toxicology reviewer, that there are no outstanding pharmacology/toxicology issues that preclude approval. No new pharmacology/toxicology studies were submitted in support of this application. The applicant referenced Drug Master Files for (b)(4) novel excipients, a strawberry flavor mixture, (b)(4) Dr. Harrouk found all three acceptable.

### **5. Clinical Pharmacology/Biopharmaceutics**

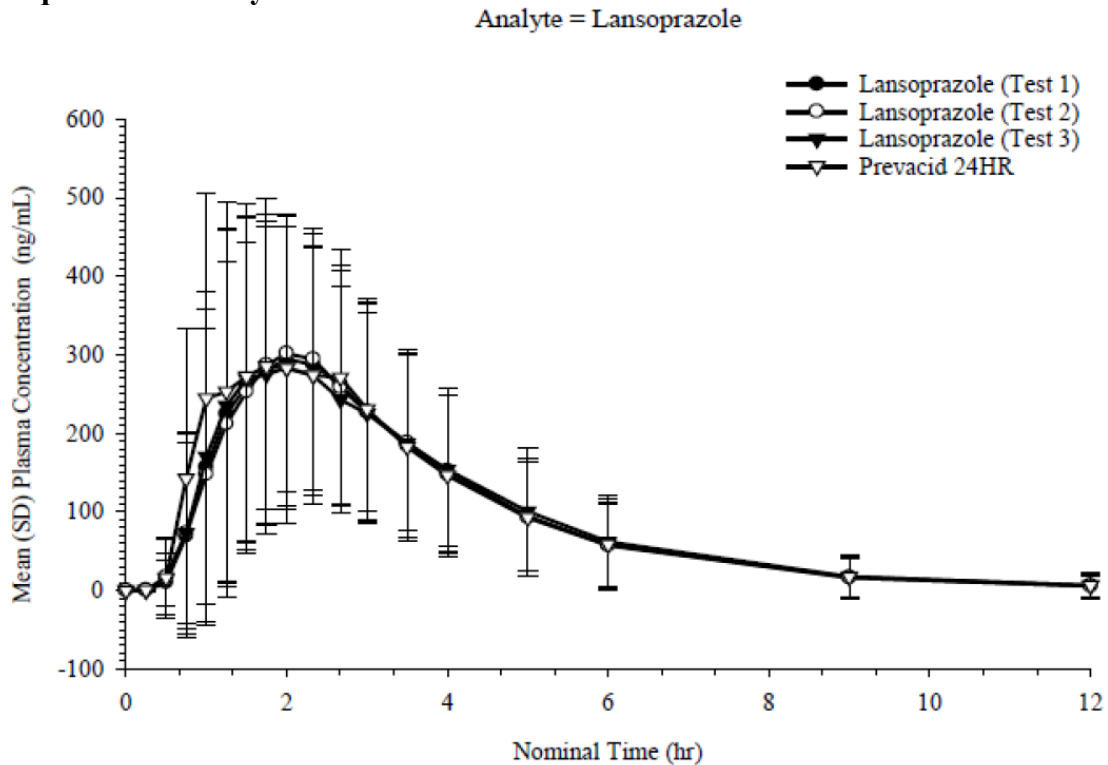
I concur with the conclusions reached by the clinical pharmacology review and the biopharmaceutics reviewer that there are no outstanding clinical pharmacology or biopharmaceutics issues that preclude approval.

A bioequivalence (BE) study was conducted in 60 healthy men and women. It was a single-center, randomized, single-dose, open-label, four-way crossover design. It compared the pharmacokinetics of the following arms:

- Treatment A: 15 mg delayed-release ODT placed on tongue until disintegration and then swallowed without water
- Treatment B: 15 mg delayed-release ODT placed on tongue until disintegration and then swallowed with water
- Treatment C: 15 mg delayed-release ODT swallowed with water
- Treatment D: 15 mg delayed-release capsule (Prevacid 24 HR) swallowed with water.

The following figure illustrates the results of the study:

**Figure 5.1: Mean Concentration-Time Profile for Lansoprazole for Each Treatment, Bioequivalence Study**



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

The following table displays the results of the study:

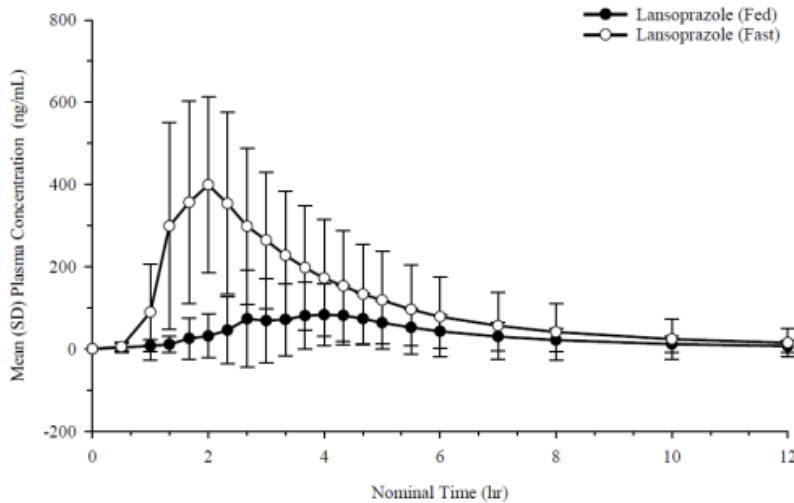
<b>Table 5.1: Bioequivalence Study Results</b>			
<b>Parameter</b>	<b>A vs D</b>	<b>B vs D</b>	<b>C vs D</b>
<b>C<sub>max</sub> (ng/mL)</b>	92.7 (83.6-102.7)	87.6 (79.0-97.2)	95.1 (85.6-105.6)
<b>AUC<sub>0-t</sub> (ng-hr/mL)</b>	94.8 (88.4-101.8)	93.9 (87.5-100.8)	97.9 (91.1-105.3)
<b>AUC<sub>0-inf</sub> (ng-hr/mL)</b>	94.8 (8.5-101.4)	93.7 (87.5-100.3)	97.7 (91.2-104.7)
Treatment A: 15 mg delayed-release ODT placed on tongue until disintegration and then swallowed without water Treatment B: 15 mg delayed-release ODT placed on tongue until disintegration and then swallowed with water Treatment C: 15 mg delayed-release ODT swallowed with water Treatment D: 15 mg delayed-release capsule (Prevacid 24 HR) swallowed with water. AUC = area under the time-concentration curve C <sub>max</sub> = maximum concentration Source: Dr. Apparaju's review, pg 6, DARRTS 2016 04 20			

All AUC values, and all C<sub>max</sub> values except for B vs D, fell within the usual acceptance boundaries (90% confidence interval 80-125%). Dr. Apparaju, the Clinical Pharmacology reviewer, stated that this observed modest decrease (lower bound 79 vs 80) in C<sub>max</sub> was unlikely to have clinical implications, especially since all AUC parameters fell within the usual acceptable range. I concur.

A food effect study was also conducted. It should be noted that, for the approval trials for both prescription Prevacid, and for OTC Prevacid 24 HR, studies were conducted with an administration direction to take the product “before eating or before breakfast”, and did not specify how long before eating. For both products, efficacy was demonstrated.

As illustrated in the following figure, food had a significant effect on the pharmacokinetics of this lansoprazole ODT product.

**Figure 5.2: Lansoprazole Concentrations under Fasted and Fed Conditions**



Source: Dr. Apparaju's review, pg 8

This represented a 70% reduction in AUC, and a 75% reduction in C<sub>max</sub>, in the fed state.

In Dr. Apparaju's first review (DARRTS 2016 04 20) for this NDA (208025), she recommended an instruction to take the product 30 minutes before eating. However, after she reviewed the earlier approval trials for the reference products, she placed an addendum in DARRTS on 16 May 2016, with the following statement:

“It appears that for earlier approvals (original prescription Prevacid and Prevacid 24 HR), the dose was administered in the clinical trials ‘before eating [REDACTED] (b) (4)’ 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 [REDACTED] (b) (4) before eating’, as this is consistent with other labels and based on precedence.”

I concur with Dr. Apparaju's amended conclusion. My logic is as follows:

- FDA previously found the nonprescription Prevacid lansoprazole 15 mg capsule to be effective enough for approval.
- For that reference capsule, two efficacy studies were done and showed efficacy, and the instruction was simply to take before eating, without a stipulation to take at least 30 minutes before eating.
- The Directions for Use in the DFL for that capsule are consistent with the method of administration used in those successful efficacy trials, and specify only that the consumer should take the capsule before eating in the morning.
- That Prevacid 24 HR capsule was the reference product to which this new tablet was compared.
- The food effects for the Prevacid capsule and this lansoprazole ODT are similar.
- There is no safety issue associated with this food effect.
- Although one might hypothesize that the response rate in the Prevacid 24 HR efficacy study might have been higher had the study been done with a 30-minute premeal instruction, we have no clinical data to support that hypothesis. The relationship between pharmacokinetics and pharmacodynamics for proton pump inhibitors is complex, and pharmacokinetics does not always correlate with pharmacodynamics.
- There is some evidence for lansoprazole that the control of gastric pH over the 24 hour period may actually be better when lansoprazole is administered right before a meal than when lansoprazole is administered fasting (Hatlebakk et al 2000).

Separately, regarding site inspection, Shila S. Nkah of the Division of New Drug Bioequivalence Evaluation in the Office of Study Integrity and Surveillance recommended that no on-site bioequivalence study inspection be conducted, because an inspection of the site had recently been conducted (DARRTS 2015 11 10).

## 6. Clinical Microbiology

I concur with the conclusions reached by the microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

## 7. Clinical/Statistical-Efficacy

No new clinical efficacy studies were conducted for this 505(b)(2) application.

## 8. Safety

No new safety signals emerged for lansoprazole in this development program. (b) (4)

Because this is an orally disintegrating tablet, the sponsor was required to conduct oropharyngeal assessments. Please see Dr. Parikh's review for a full description of those assessments. Across both the BE and food effect studies, for a total of 90 subjects, 3 subjects experienced minor oropharyngeal erythema, which resolved prior to end of study in all 3 cases.

## 9. Advisory Committee Meeting

Not applicable.

## 10. Pediatrics

The sponsor requested a full waiver, and FDA granted it on this basis:

Per section 505(B)(a)(4)(A)(ii) of the Federal Food, Drug and Cosmetic Act, "there is evidence strongly suggesting that nonprescription lansoprazole would be ineffective and unsafe in all pediatric age groups". The underlying causes for heartburn in children should be evaluated by a healthcare professional. For the pediatric population, proton pump inhibitors should be available only by prescription.

The proposed Drug Facts label limits use to those 18 years of age and older.

## 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.



## 12. Labeling

CPT Mary Vienna (DNDP Interdisciplinary Science reviewer) and Dr. Grace Jones (Division of Medication Error Prevention and Analysis reviewer) each reviewed the labeling, and DNDP requested several changes, with which Dexcel complied. See CPT Vienna's and Dr. Jones' review for details. Some of the requested changes included:

- On the principal display panel (PDP), removal of [REDACTED] (b)(4) from near an image of the tablet, to reduce the likelihood of dose confusion
- Increase in prominence of the font for the established name on the PDP
- Addition of this statement to the blister labels - "Keep the carton and package insert. They contain important information."
- Separation of a complex bullet in the Directions for Use into two bullets
- Addition of a statement to the section on use by children that instructs consumers to ask a doctor before use if considering the product for children
- Addition of a toll-free number for consumers to call with questions

Initially, CPT Vienna expressed concern about a 7-count blister presentation, because proton pump inhibitors are specifically approved for a 14-day course of treatment. However, upon further review, she noted that there are approved 7-count blisters for Prilosec OTC (NDA 21229) and omeprazole (NDA 22032), and therefore, she amended her review and found the 7-count blister card acceptable. The 7-count blister card will not be marketed separately, but will be presented as two 7-count blisters within one carton, for a total count of 14 doses.

Dexcel did not propose a proprietary name.

## 13. Decision/Action/Risk Benefit Assessment

I recommend approval of this application.

I concur with Dr. Becker's risk: benefit assessment as stated in his cross-discipline team leader review. Frequent heartburn, while not life-threatening, results in pain, loss of sleep and other morbidity. Lansoprazole 15 mg is effective in relieving the symptoms of frequent heartburn. This new orally disintegrating tablet does not present additional risk compared to currently available proton pump inhibitors, and may have some benefit in terms of the convenience of being able to take the ODT without water.

In addition to Dr. Becker's recommendation for approval, all other review disciplines also recommended approval.

### Reference:

Hatlebakk, J et al 2000. Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. *Aliment Pharmacol Ther* 14:1267-72

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KAREN M MAHONEY  
06/07/2016