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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number: 208-025

Supporting Document/s: S000 (original submission) (b) (4)
after refusal to file)

Applicant's Letter Date: December 5, 2014; August 6, 2015

CDER Stamp Date: December 8, 2014; August 7, 2015

Product: Lansoprazole Delayed-Release Orally
Disintegrating Tablets, 15 mg

Indication: Relief of heartburn

Applicant: Dexcel Pharma Technologies (DPT; a subsidiary
of Pfizer, Inc.)

Review Division: Division of Nonprescription Drug Products (DNDP)

Primary Reviewer: Wafa Harrouk, PhD

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Disclaimer

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Any information or data necessary for approval of NDA 208-025 that the applicant does not own or have a written right to reference constitutes one of the following: (1) published literature or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are included for descriptive purposes only and are not relied upon for approval of NDA 208-025.

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1 Executive Summary

1.1 Introduction

This New Drug Application (NDA 208-025) is a 505(b)(2) application which has been submitted by Dexcel Pharma Technologies (DPT; a subsidiary of Pfizer, Inc.) to obtain marketing approval for the Over The Counter (OTC) use of 15 mg Lansoprazole Delayed Release (DR) Orally disintegrating Tablets (ODT) for the relief of symptoms associated with frequent heartburn in adults 18 years and older (referenced thereafter as Lansoprazole DR ODT) . The applicant did not conduct new nonclinical studies to support approval of this NDA but is relying on the nonclinical safety which was provided for the approval of the listed drug, Prevacid® (NDA 20-406).

1.2 Brief Discussion of Nonclinical Findings

No new studies were submitted in support of the approval of NDA 208-025. The sponsor is referencing NDA 20-406 for pharmacology and toxicology information to support the safety of the proposed product from the nonclinical perspective.

1.3 Recommendations

Approvability

Pharmacology/Toxicology recommends an approval action for NDA 208-025.

2 Drug Information

2.1 Drug

CAS Registry Number: 103577-45-3

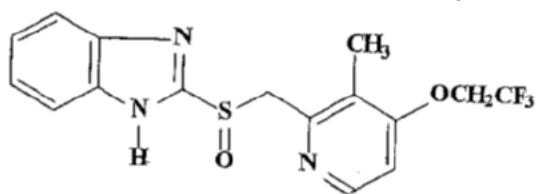
Generic Name: Lansoprazole

Code Name: None

Chemical Name: 2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl)-1H-benzodimidazole

Molecular Formula/Molecular Weight: C₁₆H₁₄F₃N₃O₂S/369.363 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Proton Pump Inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

The sponsor is relying on FDA’s findings of nonclinical safety in NDA 20-406 for Prevacid. Nonclinical information included in this review was obtained from the publicly available label for NDA 20-406.

Letters of authorization were obtained for the active ingredient, Lansoprazole; as well as for the excipients, (b) (4) and the artificial strawberry flavor (see table below) for the following DMFs:

Table 1 Active Pharmaceutical Ingredient – Type II DMF

DMF	API	DMF Holder
(b) (4)	Lansoprazole, USP	(b) (4)

Table 2 Excipients – Type IV DMF

DMF	Excipient	DMF Holder
(b) (4)		

2.3 Drug Formulation

The drug consists of (b) (4) the active substance, Lansoprazole, mixed with excipients to form a tablet which disintegrates when placed

on the tongue (See the composition of the final (b) (4) tablet formulation in Table 2 below).

2.4 Comments on Novel Excipients

All inactive ingredients used in manufacturing the primary tablets of lansoprazole DR ODT were found 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 USP/NF ingredients and are not listed in the IID under these names; however, their individual sub-ingredients are all listed in the IID (see Tables 3, 4 & 5 below).

The sponsor provided individual letters of authorization for the DMFs for these excipients (see section 2.2. above) as well as a qualitative and quantitative composition of the (b) (4) excipients' mixture (see Table 3-5, respectively), all of which fall within the acceptable levels in the IID list.

The strawberry flavor (b) (4) are all within the maximum potency in the IID.

The sponsor provided a safety evaluation for the (b) (4) excipients showing acceptable daily safety margins according to the IID list.

Table 2 Lansoprazole DR ODT 15 mg, Final Tablet Composition

Ingredient	Weight per tablet\ (mg)	Function	Quality Standard
(b) (4)			
Crospovidone	(b) (4)	(b) (4)	NF
Sucralose			NF
Ascorbic Acid			USP
Strawberry flavor (b) (4)			DMF holder standard
Colloidal Silicon Dioxide			NF
Sodium Stearyl Fumarate			NF
Total tablet weight			248.0

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

2.5 Comments on Impurities/Degradants of Concern

Stability results for long-term ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\%$ Relative Humidity (RH)) and accelerated ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\%$ RH) storage conditions were conducted. Three impurities resulting from potential degradation were identified (see table below). All impurities were within the ICH requirements for impurities/degradants. An increase in

the total impurities level was observed at accelerated conditions but levels did not exceed the ICH specification levels.

List of Impurities and Sources in Lansoprazole Delayed-Release Orally Disintegration Tablets, 15 mg

IUPAC Chemical Name	Code	Chemical Structure	Degradation Product
(b) (4)			

Based on the stability results, the sponsor is proposing a shelf-life of 24 months for Lansoprazole DR ODT 15 mg (further details can be found in the Quality review).

2.6 Proposed Clinical Population and Dosing Regimen

DPT is seeking approval of Lansoprazole DR ODT 15 mg for the treatment of frequent heartburn by adults 18 years or older. Lansoprazole 15 mg DR ODT is indicated for once daily administration, before eating in the morning, for a 14-day course of treatment. The tablet should be placed on the tongue and allowed to disintegrate, with or without water, until the particles can be swallowed. Alternatively, the tablet can be swallowed whole with a drink of water. The tablet should not be broken, crushed, or chewed.

2.7 Regulatory Background

DPT did not conduct any pharmacology, pharmacokinetics or toxicology studies in support of NDA 208-025 but is relying on FDA's findings of nonclinical safety of Prevacid as the listed drug product under NDA 20-406 (505 (b)(2) pathway). A pre-IND meeting was held on 25 October 2013 where the FDA agreed to this approach barring evidence of new pharmacokinetic/dynamic profiles or new toxicity findings.

DPT had originally submitted this NDA on 12/05/2014 but was sent a "refuse to file" letter due to deficiencies in the format and contents of the clinical data. Pharm/Tox did not have any "refuse to file" recommendation in the original NDA submission. The NDA was resubmitted on 8/27/2015 where it was deemed acceptable for review by DNNDP.

3 Studies Submitted

3.1 Studies Reviewed

No new studies were submitted by DPT in support of this NDA.

The applicant provided safety evaluation reports for ascorbic acid, maltitol, cetyl alcohol and hypromellose phthalate to support the use of these excipients in an ODT formulation.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Refer to the following Pharm/Tox filing reviews in DARRTS for NDA 208-025 dated 1/29/2015 (first submission) and 9/18/2015 (current submission).

4 Integrated Summary and Safety Evaluation

DPT is seeking approval of Lansoprazole DR ODT 15 mg for the treatment of frequent heartburn by adults 18 years or older for once daily administration over the course of

14-day treatment period. The applicant is relying on nonclinical data obtained for the previously approved lansoprazole product under NDA 20-406.

No new nonclinical studies were submitted in support of the approval of the current NDA. No new data were identified that would require new nonclinical studies to be conducted in order to support the approval of this NDA.

All inactive ingredients used in manufacturing the primary tablets of lansoprazole DR ODT were found 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 USP/NF ingredients and are not listed in the IID under these names; however, their individual sub-ingredients are all listed in the IID (see Tables 3, 4 & 5 below). The sponsor provided individual letters of authorization for the DMFs for these excipients (see section 2.2. above) as well as a qualitative and quantitative composition of the (b) (4) excipients' mixture (see Table 3-5, respectively), all of which fall within the acceptable levels in the IID list. The strawberry flavor is found in the IID at the same level under a different name. Stability testing resulted in the identification of three impurities, due to potential degradation were identified under accelerated conditions, all of which were within the ICH requirements for impurities/degradants.

The applicant provided safety evaluation reports for ascorbic acid, maltitol, cetyl alcohol and hypromellose phthalate to support the use of these excipients in an ODT formulation. All of these excipients have been used in other oral dosage forms (e.g., tablets, capsules) but have not been used in ODT formulations prior to this NDA. A review of the provided evaluations did not detect any new studies where the safety of the excipients was explored in the context of an ODT dosage form. While the evaluations provided adequate safety margins for the safe use following oral exposure to these excipients in the proposed product, none of them included data relevant to the specific exposure to the oral cavity (i.e., buccal) as opposed to oral gavage or dietary exposure to these ingredients. Buccal studies are not required because of the fast dissolving action of the proposed formulation. All excipients used in the formulation are qualified to be used via the oral route of administration.

The following summary of the nonclinical data (general toxicity, genetic toxicology, carcinogenicity and reproductive toxicity) for lansoprazole was obtained from the latest label for Lansoprazole (NDA 20406/S-080 dated 12/18/2015).

Lansoprazole is labeled pregnancy Category B. Reproduction studies (oral route) were performed in pregnant rats at doses up to 150mg/kg/day and in pregnant rabbits at doses up to 30 mg/kg/day. No evidence of impaired fertility or harm to the fetus at any of the doses tested was seen as a result of treatment with lansoprazole.

Lansoprazole was positive in the Ames test and the in vitro human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the ex vivo rat hepatocyte unscheduled DNA synthesis test, the in vivo mouse micronucleus test, or the rat bone marrow cell chromosomal aberration test.

Lansoprazole was tested in two separate carcinogenicity bioassays (24 months of duration) as well as in a 26- week transgenic mouse bioassay.

In the first carcinogenicity bioassay, Sprague-Dawley rats treated with oral lansoprazole (doses ranging from 5 to 150 mg/kg/day) produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. An increase in the incidence of intestinal metaplasia of the gastric epithelium was also noted in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

In the second carcinogenicity bioassay, CD-1 mice treated with oral lansoprazole (doses ranging from 15 to 600 mg/kg/day) showed a dose-related increased in the incidence of gastric ECL cell hyperplasia. An increased incidence in liver tumors (hepatocellular adenoma plus carcinoma) was also noted. The tumor incidences in male mice treated with 300 and 600 mg/kg/day and female mice treated with 150 to 600 mg/kg/day exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day.

A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Based on the information reviewed in this application, Lansoprazole DR ODT 15mg is approvable from a Pharmacology/Toxicology perspective.

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/s/

WAFA HARROUK
04/25/2016

JANE J SOHN
04/25/2016
I concur.

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/s/

WAFA HARROUK
09/18/2015

PAUL C BROWN
09/18/2015