

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208025Orig1s000

MEDICAL REVIEW(S)

Medical Officer Review of Clinical Safety Update

NDA Number(s)/Submission: NDA 208025 /Supporting Document Number (SDN) 7

Orig-1, Type 5, Sequence 0007

Trade/Drug Name: Lansoprazole Orally Dissolving Tablets (b) (4) mg

Date Received: 12/04/2015

Date Completed: 05/16/2016

Sponsor: Dexcel Pharma Technologies LTD

Reviewer: Ketan P. Parikh, M.D., Medical Officer, Division of Nonprescription Drug Products (DNNDP); FDA/CDER/OND/ODEIV/DNDP

SUMMARY:

- (1) Is an action necessary based on safety review of this submission: Yes: No:
- (a) If yes, please identify the basis for which further action is necessary:
- i. Newly identified serious adverse event: Yes: No:
 - ii. Increase in frequency or severity of labeled adverse event: Yes: No:
 - iii. Adverse event identified for monitoring at post-approval safety conference: Yes: No:
- (b) Is follow up by the Safety RPM indicated: Yes: No:
- (c) Is an OSE Consult recommended: Yes: No:

REVIEW:

The sponsor submitted Orig-1 Sequence 0007 which contains 120-Day Clinical Safety Update which will be addressed in the NDA Clinical Review by this Medical Officer.

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

/s/

KETAN P PARIKH
05/16/2016

Clinical Review
 Ketan P. Parikh, M.D.
 NDA 208025 / SN 0004
 Lansoprazole Delayed-Release Orally-Disintegrating Tablets

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	208025
Priority or Standard	Standard
Submit Date(s)	August 6, 2015
Received Date(s)	August 7, 2015
PDUFA Goal Date	June 7, 2016
Division/Office	Division of Nonprescription Drug Products (DNBP)
Reviewer Name(s)	Ketan P. Parikh, M.D.
Review Completion Date	
Established Name	Lansoprazole
(Proposed) Trade Name	
Applicant	Dexcel Pharma Technologies Limited
Formulation(s)	Delayed-release orally-disintegrating tablets
Dosing Regimen	15 mg once daily for 14 days; 14 days course may be repeated every 4 months
Applicant Proposed Indication(s)/Population(s)	Treatment of frequent heartburn (occurs 2 or more days a week)
Recommendation on Regulatory Action	
Recommended Indication(s)/Population(s) (if applicable)	Age ≥ 18

Table of Contents

Glossary.....	7
1 Executive Summary	10
1.1. Product Introduction.....	10
1.2. Conclusions on the Substantial Evidence of Effectiveness	11
1.3. Benefit-Risk Assessment	12
2 Therapeutic Context	15
2.1. Analysis of Condition.....	15
2.2. Analysis of Current Treatment Options	16
3 Regulatory Background	17
3.1. U.S. Regulatory Actions and Marketing History.....	17
3.2. Summary of Presubmission/Submission Regulatory Activity	18
3.3. Foreign Regulatory Actions and Marketing History.....	21
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	22
4.1. Office of Scientific Investigations (OSI)	22
4.2. Product Quality	23
4.3. Clinical Microbiology	25
4.4. Nonclinical Pharmacology/Toxicology	25
4.5. Clinical Pharmacology	26
4.5.1. Mechanism of Action	26
4.5.2. Pharmacodynamics.....	26
4.5.3. Pharmacokinetics.....	27
4.6. Devices and Companion Diagnostic Issues	29
4.7. Consumer Study Reviews.....	29
5 Sources of Clinical Data and Review Strategy	29
5.1. Table of Clinical Studies.....	29
5.2. Review Strategy.....	30
6 Review of Relevant Individual Trials Used to Support Efficacy	30
6.1. Project 120383: Randomized, open-label, 4-way crossover design, bioequivalence study of lansoprazole delayed-release orally disintegrating tablet 15 mg (DPT) and Prevacid [®] 24HR (LD) following a 15 mg dose in healthy subjects under fasting conditions.	30
6.1.1. Study Design.....	31
6.1.2. Study Results.....	32
6.2. Randomized, open-label, 2-way crossover design, comparative bioavailability, food-effect study of lansoprazole delayed-release orally disintegrating tablet 15 mg (Dexcel Pharma Technologies Limited).	34
6.2.1. Study Design.....	34
6.2.2. Study Results.....	35
7 Integrated Review of Effectiveness	37
7.1. Assessment of Efficacy Across Trials	37

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

7.1.1. Primary Endpoints.....	37
7.1.2. Secondary and Other Endpoints.....	37
7.1.3. Subpopulations.....	37
7.1.4. Dose and Dose-Response.....	38
7.1.5. Onset, Duration, and Durability of Efficacy Effects.....	38
7.2. Additional Efficacy Considerations.....	38
7.2.1. Considerations on Benefit in the Postmarket Setting.....	38
7.3. Integrated Assessment of Effectiveness.....	38
8 Review of Safety.....	38
8.1. Safety Review Approach.....	38
8.2. <i>Review of the Safety Database</i>	40
8.2.1. Overall Exposure.....	40
8.2.2. Relevant characteristics of the safety population:.....	41
8.2.3. Adequacy of the safety database:.....	43
8.3. Adequacy of Applicant’s Clinical Safety Assessments.....	43
8.3.1. Issues Regarding Data Integrity and Submission Quality.....	43
8.3.2. Categorization of Adverse Events.....	43
8.3.3. Routine Clinical Tests.....	44
8.4. Safety Results.....	44
8.4.1. Deaths.....	45
8.4.2. Serious Adverse Events.....	45
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects.....	45
8.4.4. Significant Adverse Events.....	45
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions.....	45
8.4.6. Laboratory Findings.....	48
8.4.7. Vital Signs.....	48
8.4.8. Electrocardiograms (ECGs).....	48
8.4.9. QT.....	49
8.4.10. Immunogenicity.....	49
8.5. Analysis of Submission-Specific Safety Issues.....	49
8.5.1. Oropharyngeal Assessments.....	50
8.6. Specific Safety Studies/Clinical Trials.....	50
8.7. Additional Safety Explorations.....	50
8.7.1. Human Carcinogenicity or Tumor Development.....	50
8.7.2. Human Reproduction and Pregnancy.....	51
8.7.3. Pediatrics and Assessment of Effects on Growth.....	54
8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound.....	54
8.8. Safety in the Postmarket Setting.....	55
8.8.1. Safety Concerns Identified Through Postmarket Experience.....	55
8.8.2. Expectations on Safety in the Postmarket Setting.....	67
8.9. Additional Safety Issues From Other Disciplines.....	68

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

8.10.	Integrated Assessment of Safety.....	68
9	Advisory Committee Meeting and Other External Consultations.....	70
10	Labeling Recommendations	70
10.1.	Prescribing Information.....	70
10.2.	Patient Labeling	71
10.3.	Nonprescription Labeling	71
11	Risk Evaluation and Mitigation Strategies (REMS)	73
11.1.	Safety Issue(s) that Warrant Consideration of a REMS.....	73
11.2.	Conditions of Use to Address Safety Issue(s)	73
11.3.	Recommendations on REMS	73
12	Postmarketing Requirements and Commitments.....	74
13	Appendices.....	74
13.1	References	74
13.2	Financial Disclosure	75

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Table of Tables

No table of figures entries found.

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Table of Figures

No table of figures entries found.

Glossary

AAPCC	American Association of Poison Control Centers
AC	Advisory Committee
AE	Adverse Event
AIN	Acute Interstitial Nephritis
AUC	Area Under Curve
BE	Bioequivalence
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	Body Surface Area
CBER	Center for Biologics Evaluation and Research
CDAD	<i>Clostridium difficile</i> -Associated Diarrhea
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
C _{max}	Maximum or Peak Serum Concentration of a drug
CMC	Chemistry, Manufacturing, and Controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Clinical Review Template
CSR	Clinical Study Report
CSS	Controlled Substance Staff
CTA	Clinical Trial Application
DAWN	Drug Abuse Warning Network
DDSR	Division of Drug Safety Research
DFL	Drug Facts Label
DMC	Data Monitoring Committee
DMEPA	Division of Medication Error Prevention and Analysis
DNDP	Division of Nonprescription Drug Products
DPT	Dexcel Pharma Technologies Limited
DSC	Drug Safety Communication
ECG	Electrocardiogram
ECL	Enterochromaffin-like
eCTD	electronic Common Technical Document
EE	Erosive Esophagitis
EMA	European Medicine Agency
ETASU	Elements to Assure Safe Use
FAERS	Food and Drug Administration Adverse Events Reporting System

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good Clinical Practices
GERD	Gastroesophageal Reflux Disease
GLP	Good Laboratory Practices
GRMP	Good Review Management Practice
H ₂ RAs	Histamine ₂ Receptor Antagonists
ICH	International Conference on Harmonization
IDS	Interdisciplinary Scientists
IEC	Independent Ethics Committee
iHC	inVentiv Health Clinique
IID	Inactive Ingredient Database
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent to Treat
IV	Intravenous
LD	Listed Drug (Prevacid 24HR [®])
MA	Market Authorization
MAH	Market Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (in UK)
mITT	modified Intent to Treat
ms	milliseconds
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NME	New molecular entity
NOL	No Objections Letter
NPDS	National Poison Data System
NSAID	Nonsteroidal Anti-Inflammatory Drugs
OCS	Office of Computational Science
ODT	Orally Dissolving Tablet
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTC	Over-The-Counter
OTR	Office of Testing and Research
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

PDF	Portable Document Format
PDUFA	Prescription Drug User Fee Act
PI	Prescribing Information
PIND	Pre-Investigational New Drug
PK	Pharmacokinetics
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PP	Per Protocol
PPI	Patient Package Insert
PPIs	Proton Pump Inhibitors
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
PSP	Pediatric Study Plan
PSUR	Periodic Safety Update Report
REMS	Risk Evaluation and Mitigation Strategy
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCLE	Subacute Cutaneous Lupus Erythematosus
SGE	Special Government Employee
SmPC	European Summary of Product Characteristics
SOC	Standard of Care
TD	Test Drug (lansoprazole delayed-release ODT 15 mg)
TEAE	Treatment Emergent Adverse Event
TGA	Therapeutic Goods Administration (Australian Regulatory Authority for drugs)
UDS	Unscheduled DNA Synthesis test
UK	United Kingdom
USA	The United States of America
VAI	Voluntary Activity Indicated
WHO	World Health Organization

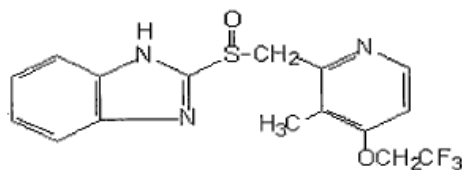
1 Executive Summary

1.1. Product Introduction

Lansoprazole belongs to the drug class of Proton Pump Inhibitors (PPIs). It is a commonly used member in its class of drugs. It relieves symptoms of heartburn by increasing gastric pH. According to the sponsor, similar to all PPIs, lansoprazole has been shown to be highly effective for suppressing intra-gastric acidity and provide 24-hour relief by specifically inhibiting the final step of the gastric acid secretion, the gastric H^+/K^+ -ATPase enzyme, in the parietal cells of the stomach. Lansoprazole's effect is dose-dependent. According to the sponsor, lansoprazole is 85% bioavailable after the first dose, which is an advantage over the other commonly used PPIs (Blum, 1996).

According to the sponsor, lansoprazole is licensed and marketed for the treatment of peptic disorders in at 92 countries, including the United States of America (USA), Europe, Canada, and Japan (Gremse, 2002). It has been approved in the USA for over 18 years and used internationally for over 30 years. The sponsor states that an excellent safety profile has been demonstrated after two decades of extensive clinical use of lansoprazole and other PPIs (Klotz, 2009).

The chemical name of lansoprazole is substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_3S$ with a molecular weight of 369.37. The structural formula is:



Lansoprazole was approved in the USA for use in adults in May 1995 as Prevacid[®], for use in children age one to 11 years in June 2002 and for use in adolescents 12 to 17 years of age in June 2004. Lansoprazole is approved for adult use in the treatment of:

- short-term treatment of symptomatic non-erosive Gastro-Esophageal Reflux Disease (GERD)
- short-term treatment of Erosive Esophagitis (EE)
- long-term maintenance of healed EE
- short-term treatment of active duodenal ulcers
- maintenance of healed duodenal ulcers
- *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

- short-term treatment of gastro-esophageal ulcers
- healing and risk reduction of Nonsteroidal Anti-inflammatory Drugs (NSAID)-associated gastro-esophageal ulcers
- treatment of pathological hyper secretory conditions including Zollinger-Ellison Syndrome

Pediatric indications for children 12-17 years of age:

- short-term treatment of symptomatic GERD
- short-term treatment of EE
- maintenance of healing EE
- treatment of pathological hyper secretory conditions including Zollinger-Ellison Syndrome

Pediatric indications for children 1-11 years of age:

- short-term treatment of symptomatic GERD
- short-term treatment of EE

The proposed indication for Test Drug (TD), lansoprazole delayed-release Orally Dissolving Tablet (ODT) 15 mg, is for the treatment of frequent heartburn (occurring 2 or more days a week) in adults 18 years of age and older. The proposed oral dosing regimen of TD is a 15 mg once daily for 14 days, with an option to repeat a 14-day course no sooner than four months. The use of this product is limited to adults over the age of 18. The sponsor will not seek pediatric indications for Over-The-Counter (OTC) marketing and requested a waiver for pediatric studies which was granted as with other OTC PPIs since OTC indication is deemed inappropriate for the pediatric population.

Medical Officer Comment:

Pediatric gastroenterologists recommend that children with symptoms of heartburn should be treated under the direction of a physician. The Agency's current position is that the treatment of heartburn in the pediatric population is not appropriate in the OTC setting and a physician should be consulted before use in children under 18 years of age. This is consistent with the OTC PPIs currently approved and marketed in the USA (i.e., omeprazole, esomeprazole, lansoprazole).

1.2. Conclusions on the Substantial Evidence of Effectiveness

From the standpoint of clinical safety, this reviewer recommends approval action for New Drug Application (NDA) 208025 lansoprazole delayed-release ODT for the relief of frequent heartburn, at the dose of 15 mg once daily for 14 days. This decision is based, in part, on review of a single bioequivalence (BE) and a single bioavailability (BA) study comparing the TD, lansoprazole ODT tablets, to the listed drug (LD), Prevacid[®] 24HR capsules. This product has an CDER Clinical Review Template 2015 Edition
Version date: June 25, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

acceptable safety profile and final approvability is contingent upon approval from the clinical pharmacology and biopharmacology standpoint as well as incorporation of the Agency's labeling recommendations for this product.

1.3. **Benefit-Risk Assessment**

According to literature (El-Serag, 2014), 18.1-27.8% of individuals in the USA have GERD. Although the condition is not life threatening, heartburn may be associated with pain, dietary restrictions, disruptions in sleep and decreased work productivity.

The benefit of the treatment with lansoprazole with non-prescription status has been weighed against safety experience in clinical trials, as well as post-marketing safety experience. Consumers have been safely self-treating heartburn with OTC PPIs beginning in 2003 in the USA when omeprazole (Prilosec[®] OTC) was approved to treat frequent heartburn. Since then, additional PPIs were approved for OTC use in 2009, lansoprazole (Prevacid[®] 24HR) and a combination of omeprazole and sodium bicarbonate (Zegerid[®] OTC), and esomeprazole magnesium (Nexium[®] 24HR Delayed-Release Capsules) received the Agency's approval for OTC use in March 2014.

The general toxicity of lansoprazole is low. Nonclinical studies have not shown any relevant reproductive toxic or genotoxic effects. Clinical long-term use of lansoprazole has not lead to any evidence of carcinogenic potential, which gives more reassurance especially considering the limited duration of treatment of 14 days, including repeat treatment courses after 4 months in the OTC setting. Lansoprazole is not known to be addictive or to have any psychotropic or narcotic characteristics. The incidence of severe or serious adverse events (AEs) following daily administration of lansoprazole 15 mg is low.

The safety and tolerability of lansoprazole are also supported by extensive postmarketing experience since the drug's launch in 1995. The majority of AEs reported were mild and transient in nature, the most frequent being include diarrhea, headache, abdominal pain, nausea, and constipation. The approved oral prescription (Rx) formulation has never been recalled from the international or domestic market for safety reasons. Lansoprazole was approved for OTC use in the USA in 2009 [Prevacid[®] 24HR, NDA 022327, Novartis Consumer Health, Inc. (Novartis)].

Efficacy

In support of this NDA, the sponsor conducted a BE (Project 120383) and a BA study (Project 120384), comparing the pharmacokinetics (PK) of a single dose of the TD with LD in healthy subjects. The sponsor did not conduct any new efficacy studies to support this NDA; efficacy of the product is extrapolated based on PK data from a single dose.

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

The PK studies (BE and BA studies) were conducted in Canada. The BE study is a single center, randomized, single-dose, open-label, 4-way crossover study with at least a seven day washout period involving 72 healthy subjects. The BA study is also a single center, randomized, single-dose, open-label, 2-way crossover study involving 18 healthy, adult subjects with at least three days washout period to compare the rate and extent of absorption of the TD under fasting and fed conditions. The inclusion and exclusion criteria are similar for both studies. The following treatments were administered for the studies:

- Lansoprazole delayed-release ODT 15 mg tablets (Dexcel Pharma)
- Prevacid® 24HR 15 mg capsules (Novartis)

In the BE study, the sponsor concluded that the TD was bioequivalent to the LD under fasting conditions, however; the TD was almost bioequivalent in Test 2 (TD allowed to dissolve over 60 seconds and particles swallowed with water) when compared to LD; the 90% geometric confidence intervals were within the acceptance range for AUC (Area Under Curve)_{0-t} and AUC_{0-inf}, but was 78.59% to 96.9% for C_{max} (Maximum or Peak Serum Concentration of a drug). The sponsor claims that it has demonstrated bioequivalence of its proposed drug with and without water, hence, the sponsor believes that the efficacy of the proposed product is supported by this demonstrated bioequivalent extent of exposure for all treatment groups in comparison to the LD. Table 1 below shows the results of key summary PK parameters for this study.

Table 1: Ratios and 90% Geometric Confidence Intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} for lansoprazole

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

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

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

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Test 1 Treatment A: TD placed on the tongue until disintegration and then swallowed without water

Test 2 Treatment B: TD placed on the tongue until disintegration and then swallowed with water

Test 3 Treatment C: TD swallowed with water

Reference D: LD swallowed with water

[Source: modified from the sponsor's submission, Table 4, p. 19 of 31, M2.7.1]

In the BA study, the sponsor concluded that a statistically significant food effect was observed following a 15 mg dose of lansoprazole ODT given the fed/fasted ratios of 23.25%, 27.03%, and 16.56%, respectively, for AUC_{0-t} , AUC_{0-inf} , and C_{max} ; the 90% of the geometric CI of the ratio A/B of least-squares means of ln-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} were not between 80.00% to 125.00%. Hence, the proposed drug must be administered in a fasting state as directed on the DFL.

Table 2: Ratios and 90% Geometric Confidence Intervals for AUC_{0-t} , AUC_{0-inf} , and C_{max} for lansoprazole

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC_{0-t}	Treatment A (Fed) - Treatment B (Fasted)	23.25%	16.11%	33.57%	67.08%	89.82%
AUC_{0-inf}	Treatment A (Fed) - Treatment B (Fasted)	27.03%	18.97%	38.52%	61.82%	90.29%
C_{max}	Treatment A (Fed) - Treatment B (Fasted)	16.56%	10.51%	26.11%	87.72%	64.16%

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

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

[Source: modified from the sponsor's submission, Table 7, p. 24 of 31, M2.7.1]

See clinical pharmacology and biopharmaceutics consult for detailed analysis of the PK studies.

Safety

In the BE study, 72 subjects were randomized out of which 60 subjects completed the entire study and the other 12 subjects completed some portions of the study. In the BA study, 18 subjects were randomized and dosed in this study; 17 subjects completed all study periods and one subject completed a portion of the study prior to withdrawal.

The sponsor submitted relevant review articles focusing on general safety for lansoprazole from 2008 to May 21, 2015; there were 30 studies that were identified from the PubMed search strategy. In addition, for the 120-Day Safety Update, the sponsor identified and reviewed four

publications pertaining to the safety of lansoprazole. According to the sponsor, overall, the AEs reported in the literature for lansoprazole were mild in nature. Some of the most commonly reported AEs were abdominal pain and headache. Literature search during the 120-Day Safety Update, a retrospective study of GERD patients exposed to PPIs reported an association between PPI use and cardiovascular complications such as myocardial infarction as well as two-fold increase in cardiovascular mortality. The study did not account for drug dosage or duration of use. The findings differ from those of another study by Rossini (Rossini, 2011) which showed that the incidence of one year major adverse cardiac events was no different between patients treated with or without PPIs. The sponsor also identified a case report of a 48-year old female who presented with Subacute Cutaneous Lupus Erythematosus (SCLE). The patient was taking lansoprazole for 2 months and symptoms resolved within a few days after discontinuation of lansoprazole. (b) (4) The Medicines and Healthcare products Regulatory Agency (MHRA) of United Kingdom (UK) and European Medicines Agency (EMA) of the European Union (EU) have recommended class labeling change for Rx and OTC PPIs effective July 2015. (b) (4)

(b) (4) The literature search also identified a small risk of *Clostridium difficile* associated diarrhea especially in hospitalized patients with lansoprazole and other OTC PPIs even with short duration of use.

Lansoprazole has a well-established animal and human safety profile. It has been marketed at the 15 mg to 60 mg/day dose for Rx use for over 21 years. Lansoprazole as an oral formulation was first approved for marketing in Europe in 1991 and in the USA in 1995, and is currently approved in over 90 countries for various acid related disorders. There is a comprehensive amount of postmarketing safety information available. Safety and tolerability of lansoprazole is well established and is supported by postmarketing experience from millions of patient-years of treatment. In addition, according to the sponsor, there are more than 10,000 patients/subjects that have been exposed to lansoprazole in clinical trials. Adverse events are most often mild and reversible and the safety profile is similar for different formulations, treatment indications, age groups and patient populations.

Medical Officer Comment:

In summary, this reviewer concludes that the risk-benefit assessment is favorable to support the approval of lansoprazole 15 mg delayed-release orally disintegrating tablets for OTC use as directed in proposed labeling: dosed once daily for 14 days for the treatment of frequent heartburn, which may be repeated no sooner than every 4 months.

2 Therapeutic Context

Analysis of Condition

Heartburn is a symptom of GERD which can occur when acidic stomach contents move into the

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

esophagus from the stomach, thereby, causing a burning sensation in the chest or throat. Acid production in the stomach is stimulated when gastrin, acetylcholine, or histamine bind to their respective receptors on the gastric parietal cell and induce the hydrogen/potassium ion adenosine triphosphatase proton pump (H^+/K^+ -ATPase) to release H^+ ions by replacing it with K^+ .

Most heartburn sufferers have events occurring both during the day and at night. In the USA, 15-20% of adults report weekly episodes of GERD and 10% of the population report daily episodes of GERD (McQuaid, 2015). Majority of the patients have mild disease. The spectrum of long-term injury from GERD includes esophagitis, stricture, Barrett's esophagus, and adenocarcinoma. Rise in the occurrence of GERD has led to increased incidence of esophageal adenocarcinoma in the USA. There were 8000 cases of adenocarcinoma reported in the USA in 2013 (Kahrilas, 2015). Some degree of GERD is normal when the lower esophageal sphincter relaxes during belching but esophagitis results from excessive reflux of gastric contents which fails to clear from the esophagus.

Common presenting symptoms of GERD include heartburn and regurgitation. Less common symptoms include chest pain and dysphagia. Chronic GERD is associated with chronic cough, laryngitis, asthma, and dental erosions (Kahrilas, 2015).

Complications of GERD include chronic esophagitis and stricture. There is relationship between GERD and esophageal adenocarcinoma. Chronic GERD is associated with Barrett's esophagus with the associated risk of esophageal adenocarcinoma. Estimated rate of cancer development from Barrett's esophagus is 0.1-0.3% per year (Kahrilas, 2015).

GERD is a clinical diagnosis. Diagnostic studies that are helpful include upper endoscopy, endoscopic ultrasound, esophageal manometry, reflux testing, and barium radiography. Diagnosis of Barrett's esophagus and esophageal adenocarcinoma requires upper endoscopy with biopsy of the lower esophagus (Kahrilas, 2015).

Treatment of GERD starts with lifestyle modifications which include avoiding foods that cause GERD, avoidance of acidic foods that are inherently irritating, and adopting behaviors that minimize reflux which include weight loss. Pharmacological treatment for GERD includes Histamine₂ receptor antagonists (H_2 RAs) and PPIs which block acid secretion. Nissen fundoplication surgery can be used to surgically correct GERD symptoms with its potential deleterious effects (Kahrilas, 2015).

2.2. Analysis of Current Treatment Options

Available OTC heartburn treatments include:

- antacids to neutralize stomach acid such as aluminum and/or magnesium

CDER Clinical Review Template 2015 Edition

Version date: June 25, 2015 for initial rollout (NME/original BLA reviews)

16

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

hydroxide, calcium bicarbonate, and sodium bicarbonate

- H₂RAs to block acid secretion such as famotidine, ranitidine, cimetidine, and nizatidine
- PPIs to block acid secretion which include:
 - omeprazole (Prilosec[®] OTC 2003)
 - lansoprazole (Prevacid[®] 24HR 2009)
 - combination of omeprazole and sodium bicarbonate (Zegerid[®] OTC 2009)
 - esomeprazole magnesium (Nexium[®] 24HR delayed-release capsules 2014)

In August 2013, a drug utilization review was conducted by Office of Surveillance and Epidemiology (OSE) which examined national sales of PPIs from year 2002 through year 2012. This review was prompted by a request from the Division of Drug Safety Research (DDSR) in the Office of Testing and Research (OTR) as part of their evaluation of the occurrence of hypomagnesemia in patients taking PPIs. From 2002 to 2012, the total number of dispensed prescriptions for PPIs increased by 52% from (b) (4) prescriptions in year 2002 to (b) (4) prescriptions in year 2012. In year 2012, OTC sales accounted for more than one-third of omeprazole sales and 47% of lansoprazole sales.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lansoprazole was approved in the USA for use in adults in May 1995 as Prevacid[®], for use in children age one to 11 years in June 2002 and for use in adolescents 12 to 17 years of age in June 2004. Lansoprazole is approved for adult use in the treatment of:

- short-term treatment of symptomatic non-erosive Gastro-Esophageal Reflux Disease (GERD)
- short-term treatment of Erosive Esophagitis (EE)
- long-term maintenance of healed EE
- short-term treatment of active duodenal ulcers
- maintenance of healed duodenal ulcers
- *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence
- short-term treatment of gastro-esophageal ulcers
- healing and risk reduction of Nonsteroidal Anti-inflammatory Drugs (NSAID)-associated gastro-esophageal ulcers
- treatment of pathological hyper secretory conditions including Zollinger-Ellison Syndrome

Lansoprazole was approved by the Agency in Rx strength as Prevacid[®] (15 mg, 30 mg) in May

Clinical Review
 Ketan P. Parikh, M.D.
 NDA 208025 / SN 0004
 Lansoprazole Delayed-Release Orally-Disintegrating Tablets

1995, Rx strength as Prevacid[®] suspension (15 mg, 30 mg) in May 2001, Rx strength as Prevacid[®] ODT (15 mg, 30 mg) in August 2002, OTC strength as Prevacid[®] 24HR (15 mg) in May 2009, and Rx strength as Prevacid[®] intravenous formulations in May 2004. In addition, it was approved for Rx as a combination drug with naproxen marketed as Prevacid[®] Naprapac in multiple strengths in November 2003.

Takeda Pharmaceuticals U.S.A., Inc. (Takeda), holder of NDA 021507 (Prevacid[®] Naprapac), NDA 021566 (Prevacid[®] IV) and NDA 021281 (Prevacid[®] Suspension) withdrew its approval for these NDA's on January 11, 2010, January 12, 2010 and March 26, 2010 respectively. The Agency acknowledged these requests through the Federal Register on June 8, 2011. Takeda withdrew the approval for marketing reasons and not due to safety concerns.

3.2. Summary of Presubmission/Submission Regulatory Activity

Dexcel Pharma Technologies Limited (DPT), the sponsor, engaged in several exchanges with the Agency during the development program for this product under the Investigational New Drug Application (IND) 118528. The following are the main points of discussion during the interactions with the sponsor:

- IND meeting on September 23, 2013:
 - The Agency agreed to 505 (b)(2) application approach as long as safety and/or effectiveness for one or more listed drugs is scientifically appropriate and the sponsor must establish a “bridge” between the proposed drug and listed drug.

Table 3: Synopsis of Key Interactions with the sponsor under IND 118528 and NDA 208025 (Lansoprazole Delayed-Release ODT)

Date	Meeting Type	Key Points or Action Items
09/23/2013	Pre-IND Type B	The following comments were conveyed to DPT: <ul style="list-style-type: none"> • BE bridging study with an approved product • Address food effect on PK for proposed formulation • <i>in vitro</i> alcohol-induced dose dumping study or justification as to why such study is not feasible • Depending on the <i>in vitro</i> testing, <i>in vivo</i> testing may be required • Safety and efficacy data may be relied upon NDA 022327 • <i>in vivo</i> disintegration time be recorded and provided in the NDA • Submit dissolution data of the drug product • Include a safety assessment of the oropharyngeal

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

		<p>area before, after study drug administration for 14 days, and just prior to discharge from the study</p> <ul style="list-style-type: none"> • Provide analysis and summary of safety information from Food and Drug Administration Adverse Events Reporting System (FAERS), World Health Organization (WHO), National Poison Data System (NPDS), and Drug Abuse Warning Network (DAWN) database as well as published literature for listed drug • Nonclinical safety data from listed drug was acceptable as long as PK/Pharmacodynamics (PD) profiles are similar to proposed drug • Proposed limits for N-oxide, sulfide, and sulfone impurities in the drug product must meet International Conference on Harmonization (ICH) Q3B limits or adequate justification to support higher limits will be required • Submit stability data from accelerated and intermediate storage conditions that meet ICH Q1A guidance • Strongly encourage the use of data standards during submission of NDA clinical and nonclinical data in .xpt or SAS format and to include an AE file as part of the NDA submission • Submit Pediatric Study Plan (PSP) 210 days prior to the submission of the NDA or earlier • OTC Drug Facts Label (DFL) does not have “Dosage and Administration” section; instead, it has a “Directions” section • Provide list of countries where the product is marketed at OTC vs. Rx, foreign labels with English translation, and whether the product or the active ingredient was ever withdrawn from the market for safety reasons
02/28/2014	Initial PSP (iPSP)	Plan submitted by DPT requesting full pediatric waiver. DPT had no plans to extrapolate efficacy from adults to pediatric population.
07/01/2014	Agreed PSP	Plan submitted by the sponsor requesting full pediatric waiver for their product.
07/10/2014	Type C written	BE was met when lansoprazole ODT was compared with

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

	responses only	LD when the product was dissolved on the tongue and swallowed without water but not when it was swallowed with water. The C_{max} value for lansoprazole ODT did not meet BE criteria for which clinical implications will need to be addressed in the proposed labeling. DPT was reminded to use labeling guidance for industry and submit proposed labeling in PDF format electronically with the NDA.
12/11/2014	Agreed PSP	The Agency accepts the sponsor's agreed PSP
12/05/2014	NDA Submission	The sponsor submits the NDA for lansoprazole delayed-release ODT
01/30/2015	Information request	The Agency emailed information request on following: <ul style="list-style-type: none"> ➤ Inner carton label ➤ Consumer information leaflet ➤ Correct font size for DFL ➤ Identify sources of all safety data ➤ Provide list of countries where the product or active ingredient is marketed with foreign labels translated in English ➤ Provide information if the product or active ingredient was ever withdrawn due to safety concerns ➤ Provide datasets for PK studies ➤ Provide Case Report Form (CRF) for all subjects in PK studies ➤ Provide updated analysis and summaries from FAERS, WHO, NPDS, and DAWN databases ➤ Provide 4 month safety update ➤ Provide copies of all the articles used as reference
02/06/2015	Refuse to File (RTF) letter	The Agency sent RTF letter to DPT which outlined deficiencies (noted above) in the NDA application precluding timely review.
03/05/2015	Type A meeting request	The sponsor requested type A meeting to discuss RTF letter with the Agency and the meeting was scheduled for April 13, 2015.
04/13/2015	Type A meeting	The following comments were conveyed to the sponsor: <ul style="list-style-type: none"> ➤ If DPT was planning to pool adverse events from treatment arm in both BA studies, then, DPT must describe the pooling strategy in the submission ➤ The Agency did not agree with single dose oropharyngeal assessments in both BA studies

		<p>since proposed product is labeled for repeated use</p> <ul style="list-style-type: none"> ➤ Safety data: provide a description of the severity of the AE, the number of AE with a serious outcome, and the associated System Organ Classifications, Preferred Terms, and verbatim terms ➤ Additional excipient information provided during this meeting may provide sufficient justification for not conducting a 14-day oropharyngeal safety assessment and that this would be review issue and not a filing issue ➤ Provide lansoprazole related safety information from DPT's, FAERS, WHO, DAWN, and NPDS databases with analysis and summary. Summary reports must contain basic demographic information, visit type and characteristics, and disposition ➤ Provide tabular summary and analysis of retrieved literature on lansoprazole focusing on safety as well as safety signals associated with other PPIs ➤ Resubmit the safety data for maltitol to the NDA ➤ If DPT chooses not to conduct an <i>in vivo</i> alcohol dose-dumping study, the lack of <i>in vivo</i> data would be a review issue rather than a filing issue. DPT will need to provide justification as why it chose not to perform <i>in vivo</i> alcohol dose-dumping PK study and address how the safety and/or efficacy of the proposed product may be compromised when used with alcohol as either a single dose or as multiple doses and how DPT plans to mitigate the risk ➤ DPT will submit proprietary name after resubmission of the NDA with understanding that there is a separate Prescription Drug User Fee Act (PDUFA) clock for proprietary name submission ➤ Decision not to list Takeda's Prevacid SoluTab as LD in the resubmission will be a review issue and not a filing issue
08/05/2015		DPT resubmits the NDA

3.3. Foreign Regulatory Actions and Marketing History

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

According to the sponsor, lansoprazole is marketed in at least 92 countries across the globe for the last 30 years and over 21 years in the USA. In 2009, Klotz (Klotz, 2009) reported excellent safety profile of lansoprazole after 20 years in the market. DPT is relying on clinical safety data generated for the approval of the LD, as well as available published literature.

There are several reports of PPI-induced acute interstitial nephritis (AIN). Most of the cases of AIN were reported in patients receiving omeprazole treatment (62 out of 65 cases reported by Medsafe in New Zealand). In 2003, the Australian Drug Reactions Advisory Committee indicated that the onset of AIN is associated with long term use of PPIs (median time to onset was 3 months, range 12-365 days). AIN warning is included in labeling of all prescription PPIs. In December 2014, the Food and Drug Administration (FDA) approved labeling changes in the prescription LD, which included AIN as a symptom of hypersensitivity reaction.

In January 2013, the Netherlands Pharmacovigilance Center reported SCLE in two patients treated with omeprazole. An additional 20 cases were later reported in the literature involving female patients between the ages of 51 and 85. Other Agencies across the world reported similar cases with lansoprazole. The safety signal led the EMA and the MHRA of UK to issue labeling changes to all PPIs (Rx and OTC) in July 2015 and August 2015 respectively. To date, the Agency has not issued a safety warning regarding SCLE and PPIs use nor implemented labeling change for PPIs.

DPT held the Marketing Authorization (MA) for lansoprazole 15 mg and 30 mg capsules in the UK and in Germany between 2006 and 2013. DPT withdrew the MA due to marketing considerations and not safety concerns.

According to the sponsor, Periodic Safety Update Report (PSUR) covering November 14, 2006 to March 14, 2011, there were 56 cases of AEs and none of them were confirmed to be associated with DPT's proposed product. In the PSUR covering March 15, 2011 to December 31, 2011, there were 56 cases of AEs and none of them were confirmed to be associated with DPT's proposed product. Until termination of pharmacovigilance activities (December 2013), there were 96 cases of AEs; only one of them was confirmed to be associated with the DPT product (Lansoprazole 15 mg capsule, in Germany): a 57-year old female (20120981 ID/ISR) who was administered 15 mg lansoprazole and experienced dyspnea, erythema, pruritus and increased blood pressure.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

On November 10, 2015, the Office of Study Integrity and Surveillance (OSIS) recommended CDER Clinical Review Template 2015 Edition
Version date: June 25, 2015 for initial rollout (NME/original BLA reviews)

22

acceptance of data without an on-site inspection. The rationale for this decision was based on recent inspection of the site and the outcome was that no action was needed.

4.2. Product Quality

According to the sponsor, lansoprazole delayed release ODT 15 mg are white to off-white mottled (with white to off-white to grayish to pinkish pellets) uncoated tablets; embossed "15" on one side. Lansoprazole delayed-release ODT contains the active ingredient lansoprazole. The ODT is comprised of (b) (4) coated pellets containing the active substance, Lansoprazole, mixed with excipients to form a tablet which during when placed on the tongue.

The unit composition of the (b) (4) coated pellets is provided in Table 4. The final (b) (4) tablet formulation is provided in Table 5 below.

Table 4: Unit Composition of (b) (4) coated Pellets

Ingredient	Weight per tablet (mg)	Function	Quality Standard
(b) (4)			
Lansoprazole	15.00	Drug substance	USP
Mannitol	(b) (4)	(b) (4)	USP
Meglumine			USP
Polysorbate 80			NF
Hypromellose (b) (4)			USP
(b) (4)			USP
			USP
			USP
			NF
Talc			USP
(b) (4)			USP
Hypromellose Phthalate (b) (4)			NF
Cetyl Alcohol			NF
Triethyl Citrate (b) (4)			NF
			USP
Titanium Dioxide (b) (4)	USP		
	NF ²		

Clinical Review
 Ketan P. Parikh, M.D.
 NDA 208025 / SN 0004
 Lansoprazole Delayed-Release Orally-Disintegrating Tablets

(b) (4)	(b) (4)
Total weight coated Tablets	(b) (4)
mg=milligrams, NF=National Formulary, USP=United States Pharmacopeia	
(b) (4)	

[Source: Sponsor's submission, M3.2.P.1 Table 1; page 3/11]

Table 5: Lansoprazole DR ODT 15 mg, Final Tablet Composition

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

[Source: Sponsor's submission, M3.2.P.1 Table 2; page 4/11]

The sponsor tested "to be marketed" product in the PK studies. The sponsor obtained lansoprazole, USP (United States Pharmacopeia) from (b) (4) certified that the methods used in, and the facilities and controls used for the manufacturing, processing, packaging, and holding of the active pharmaceutical ingredient lansoprazole were conforming to current Good Manufacturing Practice (cGMP) regulations in accordance with 21 Code of Federal Regulations (CFR) parts 210, 211, EU cGMP Part II, and ICH Q7. The sponsor refers the manufacturing process to DMF # (b) (4) which was included in the submission. Prior to use, the sponsor tested lansoprazole, USP for impurities (b) (4) according to the USP monograph for lansoprazole with additional in-house methods for impurity profile of the samples. As per the Agency's Information Request letter dated December 23, 2015, the sponsor updated the reporting of total impurities to (b) (4) decimal places. The sponsor specified tests and methods that were used to assess impurities as requested by the Agency. The sponsor used USP reference standards and materials, closure system, and assess stability.

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Medical Officer Comment

For further detail regarding the nonclinical data, please refer to the pharmacology/toxicology review, which had not been finalized at the time this clinical review was completed.

4.3. Clinical Microbiology

No new information is provided.

4.4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical or toxicology data submitted to support this NDA. The sponsor is relying on the nonclinical pharmacology and toxicology information of LD, Prevacid 24HR[®] (NDA 022327, Novartis) to support approval of its OTC lansoprazole delayed-release ODT. The nonclinical summaries for LD were referenced to the original NDA 020406 for Prevacid Rx by Novartis. Novartis provided full toxicity profile of the compound in rats and mice in repeat dose studies up to 1200 and 4800 times the clinical dosages, respectively. The safety margins based on total systemic exposure have been established by Novartis in sub-chronic toxicology studies in four species and in chronic studies in one species. The sponsor listed and reviewed available literature to support the safety of lansoprazole.

There are four excipients which are not yet approved in ODT formulation. The sponsor has provided safety evaluation report which indicates a safety margin of over (b) (4) for ascorbic acid, (b) (4) for maltitol, over (b) (4) for cetyl alcohol, and over (b) (4) for hypromellose phthalate. The sponsor provided safety evaluation reports for local (buccal) and systemic exposure to ascorbic acid, maltitol, hypromellose phthalate and cetyl alcohol as inactive ingredients in its lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and deemed it as safe and qualified for their intended use. According to the sponsor, ascorbic acid and maltitol are not listed in the approved ODT formulations according to the Inactive Ingredients Database (IID), but both ingredients are approved for oral suspensions and oral solutions according to the IID. Ascorbic acid is an inactive ingredient used at a level of (b) (4) mg (b) (4)% in the TD formulation. The allowable maximum level in the IID is (b) (4) mg for an approved oral dosage form (Moviprep[®] and Trileptal[®]). Maltitol amount in the TD is (b) (4) mg and IID allowable maximum is (b) (4) mg for an oral dosage form. Maltitol is also approved for use in oral solution and suspension drug products where direct and residual buccal contact would be expected according to the sponsor (PhosLo[®], Baraclude[®], and Keppra[®] contain (b) (4) g respectively). According to the sponsor, hypromellose phthalate (b) (4) TD contains (b) (4) mg which is (b) (4) fold less than oral formulations containing hypromellose phthalate approved by the Agency for oral granules in Biaxin[®] suspension (NDA 050698). Lastly, the sponsor states that cetyl alcohol content in its TD is (b) (4) fold less than current maximum exposure of (b) (4) mg in amoxicillin/clavulanate and diclofenac oral tablets, both which have the potential for oropharyngeal cavity exposure during daily

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

dosing up to 10 days.

Medical Officer Comment:

Lansoprazole is characterized as Pregnancy Category B. The proposed labeling addressing the use in pregnant women is acceptable. For further detail regarding the nonclinical data, please refer to the pharmacology/toxicology review, which had not been finalized at the time this clinical review was completed.

4.5. Clinical Pharmacology

No new clinical pharmacology data were generated from the BA and BE studies.

4.5.1. Mechanism of Action

Lansoprazole is a proton pump inhibitor which reduces gastric acid secretion through inactivation of the final step of the gastric acid secretion pathway in the gastric parietal cells with a dose-dependent response which leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. Lansoprazole specifically inhibits the (H⁺, K⁺)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Lansoprazole does not exhibit anticholinergic or histamine type-2 antagonist activity according to the Prevacid Rx label.

4.5.2. Pharmacodynamics

No new data were generated from the BA and BE studies. According to the sponsor, Prevacid 24HR[®] was approved via 505 (b)(1) pathway. Novartis did not conduct any nonclinical or PK studies; instead they relied on the data generated in the original application for Prevacid[®] Capsules (NDA 020406, Takeda). The sponsor is relying on data available for the LD, Prevacid 24HR[®] (NDA 022327, Novartis). The sponsor states that the Agency's Division of Nonprescription Drug Products allowed this approach, barring evidence of new pharmacokinetic/dynamic profiles or toxicity patterns, in the Pre-IND Meeting Minutes (October 25, 2013, response to Question 9).

According to the Prevacid[®] Rx label, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and the percent of time the gastric pH was >3 and >4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. Lansoprazole inhibited the normal increase in secretion volume, acidity, and acid output induced by insulin. In an intragastric pH study, increased gastric pH was seen within 2-3 hours of initial lansoprazole 15 mg administration. In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with 15 to 60 mg of oral lansoprazole. These elevations reached a plateau within two months of therapy and returned

to pretreatment levels within four weeks after discontinuation of therapy.

4.5.3. Pharmacokinetics

According to the sponsor, lansoprazole absorption is rapid and relatively complete, with mean peak plasma concentrations (C_{max}) occurring approximately 1.7 hours after oral dose administration, with absolute bioavailability exceeding 80%. C_{max} and the area under the plasma concentration-time curve (AUC) of lansoprazole are approximately dose-proportional after single-dose oral administration. Lansoprazole does not accumulate and pharmacokinetics are unaltered by multiple-dose administration. Lansoprazole is 97% bound to plasma proteins and is extensively metabolized via cytochrome P450 system (CYP2C19, CYP3A4/5) to hydroxylated sulfinyl and sulfone derivatives with little or no anti-secretory activity. According to the Prevacid Rx label, a study with single-dose oral administration of lansoprazole found almost no unchanged lansoprazole is excreted in the urine.

Special Populations

Pediatric use:

The sponsor does not intend to market its product to pediatric population. According to the Prevacid[®] Rx label, lansoprazole pharmacokinetics in pediatric patients aged 1 to 17 years were similar to those observed in healthy adult subjects.

Geriatric Use:

According to the Prevacid Rx label, the clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in the accumulation of lansoprazole. No dosage adjustment is necessary in the elderly.

Renal Impairment:

According to the Prevacid Rx label, no dosage adjustment is necessary in patients with renal impairment. Patients with renal impairment had a shortened elimination half-life and decreased total AUC (free and bound). The AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment; and the C_{max} and T_{max} (time to reach the maximum concentration) were not different than the C_{max} and T_{max} from subjects with normal renal function.

Hepatic Impairment:

According to the Prevacid Rx label, patients with various degrees of chronic hepatic impairment, the mean plasma half-life was prolonged from 1.5 - 3.2 hours to 7.2 hours. An increase in the mean AUC of up to 500% was observed at steady state in hepatically-impaired

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

patients compared to healthy subjects. Consider dose reduction in patients with severe hepatic impairment.

Gender:

According to the Prevacid Rx label, no gender differences were found in pharmacokinetics and intragastric pH results.

Alcohol:

The sponsor requests a waiver of the *in vivo* alcohol dose dumping study for this NDA since its product is designed to release all at once but delayed, avoiding the acid environment of the stomach and releasing the drug in the small intestine since lansoprazole is unstable in an acidic environment, and has very low solubility in pH <7. An *in vitro* alcohol dose dumping study demonstrated premature release of lansoprazole with alcohol at concentrations of ≥ 40%, i.e., a shot of alcohol, but not a glass of wine (wine generally contains 11.5% alcohol) or beer (5% alcohol). The sponsor reports that 5%, 10%, and 20% alcohol did not impact lansoprazole release in acidic stage. In case of higher alcohol concentrations, the product's (b) (4) coating is compromised, and the *in vivo* results will be a premature release of drug in the stomach. Lansoprazole is an acid-labile drug, exposure of the drug to this gastric acid will lead to degradation of lansoprazole and result in an ineffective drug but it will not affect the safety of the drug. The most critical hours are in the morning, since the drug should be taken in the morning before eating. It is the sponsor's opinion that *in vitro* dose dumping assessment adequately demonstrated no new safety concern that requires additional *in vivo* dose dumping study and no additional knowledge will be gained beyond that summarized above. In order to reduce the possibility of loss of efficacy due to co-administration with alcohol, a clear instruction "not to take this medicine with alcohol" is included in the proposed labeling.

Medical Officer Comment:

Taking the administration time and the effect of alcohol in to account, the worst case scenario would be lack of efficacy but not safety, especially if the patient consumes an alcoholic beverage in the morning of each day during the 14-day treatment course. This issue is appropriately addressed by the sponsor on the DFL under the "Directions" section with a statement: "do not take this medicine with alcohol".

Drug-Drug Interactions:

According to the Prevacid Rx label, lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects.

Medical Officer Comment

CDER Clinical Review Template 2015 Edition
Version date: June 25, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

The proposed label appropriately addresses the drug-drug interactions in “Ask a doctor or pharmacist before use if you are taking” section. This section was compared to listed drug DFL; both are identical and appropriately address the drug-drug interactions. For further detail regarding the nonclinical data, please refer to the clinical pharmacology and biopharmacology review, which had not been finalized at the time this clinical review was completed.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

No studies were required.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The following are the sources of clinical data submitted with this 505(b)(2) application:

- A BE study project number 120383
- A BA study project number 120384
- Summary of safety analysis of LD from the following databases:
 - FAERS, DAWN, NPDS, and WHO between 2008 and July 2015
 - 120-day safety update submitted December 4, 2015

The sponsor conducted a single BE study comparing the TD (lansoprazole delayed-release ODT 15 mg) to the LD (Prevacid[®] 24HR 15 mg capsules) and effect of food on BA of the TD to the LD.

Table 6 : Table of Clinical Trials

Type of study	Study identifier	Objective of the study	Study design	Treatment groups	Duration of treatment	Subjects (healthy volunteers)
BE	120383 Canada	Fasting BE of TD vs. LD	4-way crossover, open-label	TD dissolve and swallow without water	Single dose	N=65
				TD dissolve and swallow with water		N= 68
				TD with water		N= 66
				LD with water		N= 62
BA	120384 Canada	Fed and fasting BA of TD	2 way crossover, open-label	TD in fasting state	Single dose	N= 18
				TD in fed state		N= 18

Source: Sponsor's submission.

5.2. Review Strategy

This clinical review focuses on the clinical safety aspect of this application, primarily the safety information from the clinical trials for this OTC program and postmarketing safety information. Reviewers in chemistry, pharmacology/toxicology, biopharmacology, and clinical pharmacology will evaluate data pertinent to their respective discipline. Labeling will be reviewed by interdisciplinary scientists (IDS) from DNDP. Lastly, acceptability of the proposed proprietary name is reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in OSE.

6 Review of Relevant Individual Trials Used to Support Efficacy

Project 120383: Randomized, open-label, 4-way crossover design, bioequivalence study of lansoprazole delayed-release orally disintegrating tablet 15 mg (DPT) and Prevacid® 24HR (LD) following a 15 mg dose in healthy subjects under fasting conditions.

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

6.1.1. Study Design

Overview and Objective

No efficacy trials were conducted for this application. One PK trial was conducted comparing TD (lansoprazole ODT 15 mg) to LD (Prevacid 24HR[®] capsules, 15 mg). In an effort to bridge efficacy, the sponsor relies on demonstrating BE between the two products, TD and LD. The LD was approved as a 505(b)(1) application on May 18, 2009 (Novartis Consumer Health, Inc., NDA 022327).

Trial Design

This was a single center, randomized, single-dose, open-label, 4-way crossover BE study to compare the rate and extent of absorption of a TD, lansoprazole ODT, with and/or without water, versus LD, Prevacid 24HR[®], under fasting conditions. A total of 72 healthy adult subjects were included in this study. Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme generated by (b) (4) (Contract Research Organization (CRO)). Subjects were confined to the (b) (4) from at least 10 hours prior to drug administration until after the 12-hour post-dose blood draw, in each period. Subjects were asked to come back to the clinical facility for return visits. The treatment phases were to be separated by washout periods of seven days.

Study Endpoints

No statistical difference between treatments by TD versus LD.

Statistical Analysis Plan

According to the sponsor, no statistical analysis of safety data was performed. The data was evaluated descriptively only.

Protocol Amendments

The sponsor reported an Amendment 1 to the protocol on January 20, 2014. In order to use a Williams design, the sequences of randomization was changed from ABCD, BCDA, CDAB, DABC to ADBC, BACD, CBDA, or DCAB. In addition, the sponsor increased the sample size to 72 subjects.

Data Quality and Integrity: Sponsor's Assurance

Fully trained staff worked in the studies and followed standard operating procedure of the CRO. In addition, principles of Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) were followed by the CRO. All clinical raw data was recorded and conserved promptly according to the sponsor. All aspects of the clinical phases of the study and its documentation (including all clinical raw data and CRFs), were subjected to quality control review by qualified, trained personnel to ensure compliance with the protocol, subject safety, and data integrity via

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

data verification and cross-checking. The quality assurance unit of the CRO audited all the data, subject safety, data integrity, and compliance with the protocols.

6.1.2. Study Results

Compliance with Good Clinical Practices

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. As required by the Canadian Regulatory Agency, a Clinical Trial Application (CTA) was submitted before the beginning of the study and a No Objection Letter (NOL) was obtained prior to dosing.

Financial Disclosure

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 as defined in 21 CFR Part 54.2(a). There were no financial disclosures that would cast doubt on the findings of the studies.

Patient Disposition

In this study, 106 subjects were screened and 78 subjects were enrolled. Seventy-two subjects were randomized and dosed in this study; of these, 60 subjects completed all of the study periods. In accordance with the protocol, data from all subjects who completed the study and for whom the PK profile was adequately characterized were used for PK and statistical analyses. Majority of the subjects withdrew from the study for personal reasons according to the sponsor. Subject 27 had an AE, dizziness, after catheter insertion. Subject 47 became pregnant despite using condom with spermicide. Subject 47 was made aware that there is lack of data regarding human fetal risk associated with lansoprazole use. Subject 47 underwent abortion 25 days following LD (Subject 47 received Treatment D which consisted of Prevacid[®] 24HR) administration in Period 2. The sponsor reported that this AE was unrelated to the study medication.

Protocol Violations/Deviations

The sponsor reported protocol deviations which included medication disintegration time of less than 60 seconds by many subjects, including one subject who allowed the TD to disintegrate rather than swallowing it as whole with water, and three subjects' TD fell out of the oral cavity onto respective subjects' clothing when oral mucosa was inspected. All three quickly picked up and swallowed the TD. Other minor deviations include:

- Four subjects were found to have tobacco products in their study rooms, however, the study protocol did allow tobacco consumption
- An extra pre-dose pharmacokinetic blood sample draw

- Observation of a clot in post-dose blood draw
- Exit procedures in subject completed 15 days after last participation
- One subject’s oral mucosa exam was omitted by error prior to discharge in Period 2
- Deviations in the blood sampling schedule, all of the delays were less than 11 minutes, majority of them were less than 5 minutes. The sponsor states that there should be no impact on the statistical analysis due to time deviations since only the actual collection times were used in the PK calculations.

Medical Officer’s comment: Above noted protocol deviations and violations are minor in nature and unlikely to raise any safety concerns.

Table of Demographic Characteristics

Table 7: Descriptive statistics of demographic data for subjects included in the pharmacokinetic population

Category		PK pop			
		Comparison (A/B) N=65	Comparison (A/D) N=68	Comparison (B/D) N=66	Comparison (C/D) N=62
Age (years)	Mean ± SD	44 ± 14	43 ± 14	44 ± 14	44 ± 14
	Range	18 - 75	18 - 75	18 - 75	20 - 75
	Median	46	45	47	46
BMI (kg/m ²)	Mean ± SD	25.20 ± 2.68	25.08 ± 2.69	25.18 ± 2.67	25.12 ± 2.70
	Range	19.02 - 29.43	19.02 - 29.43	19.02 - 29.43	19.02 - 29.43
	Median	25.56	25.51	25.55	25.46
Height (cm)	Mean ± SD	167.3 ± 9.0	167.5 ± 8.9	167.3 ± 8.9	167.1 ± 9.0
	Range	151.5 - 185.0	151.5 - 185.0	151.5 - 185.0	151.5 - 185.0
	Median	167.0	167.3	166.8	166.3
Weight (kg)	Mean ± SD	70.92 ± 11.78	70.68 ± 11.62	70.81 ± 11.72	70.47 ± 11.89
	Range	49.30 - 100.10	49.30 - 100.10	49.30 - 100.10	49.30 - 100.10
	Median	69.20	69.05	69.05	68.15

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

[Source: modified from the sponsor’s submission, Project 120383, M5.3.1.2 Table 11.2-1; page 33/212.]

Efficacy Results – Primary Endpoint

No pivotal efficacy studies were conducted for this NDA. A PK study was conducted to establish bioequivalence and bioavailability between TD and LD.

Data Quality and Integrity – Reviewers’ Assessment

The Division of New Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance recommended accepting data without an on-site inspection since last inspection of

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

this site was voluntary activity indicated (VAI).

Efficacy Results – Secondary and other relevant endpoints

Not applicable.

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

6.2. Randomized, open-label, 2-way crossover design, comparative bioavailability, food-effect study of lansoprazole delayed-release orally disintegrating tablet 15 mg (Dexcel Pharma Technologies Limited).

6.2.1. Study Design

Overview and Objective

No efficacy trials were conducted for this application. One PK trial was conducted comparing TD (lansoprazole ODT 15 mg) to LD (Prevacid 24HR[®] capsules, 15 mg). In an effort to bridge efficacy, the sponsor relies on demonstrating BA between the two products, TD and LD. The LD was approved as a 505(b)(1) application on May 18, 2009 (NDA 022327, Novartis). The objective of this study was to assess the effect of food on the BA of TD administered as one dose under fasting and fed conditions.

Trial Design

This was a single center, randomized, single-dose, open-label, 2-way crossover comparative BA study to compare the rate and extent of absorption of TD under fasting and fed conditions. A total of 18 healthy, adult subjects were included in this study. Prior to study commencement, subjects were randomly assigned to a treatment group in accordance with the randomization scheme generated by the CRO. Subjects were confined in the CRO facility from at least 11 hours prior to drug administration until 12 hours post-dose blood draw, in each study period. The treatment phases were separated by a washout period of at least three days.

Study Endpoints

CDER Clinical Review Template 2015 Edition
Version date: June 25, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

No statistical difference in BA of TD versus LD in fasting and fed conditions.

Statistical Analysis Plan

Pharmacokinetic analyses were performed at the CRO. Pharmacokinetic and statistical analyses were performed using Pharsight[®] Knowledgebase ServerTM (PKS) version 4.0.2 and WinNonlin[®] 5.3, which were validated for bioequivalence studies by the CRO. These software programs perform non compartmental analyses of pharmacokinetic parameters and statistical analyses (via SAS version 9.2) according to current regulatory recommendations.

The number of observations (N), mean, standard deviation (SD), coefficient of variation (CV (%)), range (min. and max.), median and geometric mean were calculated for plasma concentrations of lansoprazole for each sampling time and treatment. These descriptive statistics were also presented for AUC_{0-t} , AUC_{0-inf} , C_{max} , residual area, T_{max} , $T_{1/2\text{el}}$, K_{el} , $K_{el\text{ lower}}$, and $K_{el\text{ upper}}$.

Protocol Amendments

None.

Data Quality and Integrity: Sponsor's Assurance

Fully trained staff worked in the studies and followed standard operating procedure of the CRO. In addition, principles of GCP and GLP were followed by the CRO. All clinical raw data was recorded and conserved promptly according to the sponsor. All aspects of the clinical phases of the study and its documentation (including all clinical raw data and CRFs), were subjected to quality control review by qualified, trained personnel to ensure compliance with the protocol, subject safety, and data integrity via data verification and cross-checking. The quality assurance unit of the CRO audited all of the data, subject safety, data integrity, and compliance with the protocols.

6.2.2. Study Results

Compliance with Good Clinical Practices

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 IEC requirements relative to clinical studies and the recommendations laid down in the most recent version of the Declaration of Helsinki. As required by the Canadian Regulatory Agency, a CTA was submitted before the beginning of the study and a NOL was obtained prior to dosing.

Financial Disclosure

The sponsor submitted the FDA Form 3454 certifying that it has not entered into any financial arrangement with the listed clinical investigator(s) whereby the value of the compensation to

the investigator(s) could be affected by the outcome of the study as defined in 21 CFR Part 54.2(a). There were no financial disclosures that would cast doubt on the findings of the study.

Patient Disposition

In this study, 32 subjects were screened and 22 subjects were enrolled and participated in Period 1 check-in procedures. Eighteen subjects were randomized and dosed in the study out of which 17 subjects completed all of the study periods. In accordance with the study protocol, data from all of the subjects who completed the study and for whom the PK profile was adequately characterized were used for PK and statistical analysis (n=17). One subject withdrew in Period 2 due to symptoms of severe headache and hot flush prior to the TD administration.

Protocol Violations/Deviations

Minor protocol deviations occurred. For example, deviations in the blood sampling schedule, a subject refused to return for repeat blood draw since initial blood sample clotted, and a subject drank 21 ounces of Coca Cola 14 hours prior to pre-dose. According to the sponsor, these deviations are unlikely to affect study results and conclusions.

Table of Demographic Characteristics

Table 7: Demographic data for subjects included in the pharmacokinetic population

Category		PK population N=17
Age (years)	Mean ± SD	48 ± 12
	Range	25 – 70
	Median	46
BMI (kg/m ²)	Mean ± SD	25.74 ± 2.16
	Range	21.20 - 29.52
	Median	25.48
Height (cm)	Mean ± SD	168.4 ± 10.1
	Range	148.5 - 190.0
	Median	169.5
Weight (kg)	Mean ± SD	73.12 ± 9.86
	Range	54.60 - 88.30
	Median	73.70

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

[Source: modified from sponsor's submission, Module 5.3.1.2, Project 120384, Table 11.2-1, p. 29/102]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was 100% as subjects were dosed under direct supervision at the CRO site. In addition, subjects were confined to the CRO site for 12 hours post-dose blood draw.

Efficacy Results – Primary Endpoint

CDER Clinical Review Template 2015 Edition

Version date: June 25, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

No pivotal efficacy studies were conducted for this NDA. A PK study was conducted to establish bioavailability between TD and LD.

Data Quality and Integrity – Reviewers’ Assessment

The Division of New Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance recommended accepting data without an on-site inspection since last inspection of this site was VAI.

Efficacy Results – Secondary and other relevant endpoints

Not applicable.

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

There were no efficacy trials conducted for this application. One PK study was conducted comparing TD with LD. To bridge efficacy, the sponsor relies on demonstrating BE and BA between the two products. The LD was approved via 505(b)(1) application on May 18, 2009 (NDA 022327, Novartis) for the treatment of frequent heartburn in adults 18 years of age or older.

7.1.2. Secondary and Other Endpoints

Not applicable.

7.1.3. Subpopulations

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

According to the sponsor, post-hoc analysis of pooled data from two clinical studies that supported the approval of the LD showed no significant differences between the younger (< 65 years) and older age groups (\geq 65 years) in response to lansoprazole treatment (Kushner, 2009). A second post-hoc pooled analysis showed no statistically significant difference in the number of heartburn-free 24-hour days during lansoprazole treatment between men and women (Kushner, 2009).

7.1.4. Dose and Dose-Response

Not applicable.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

According to the sponsor, tolerance has not been reported for the LD, therefore, tolerance will not develop for individuals administered the TD.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Not applicable.

7.3. Integrated Assessment of Effectiveness

According to the sponsor, the efficacy of 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 (Kushner, 2009) (Peura, 2009).

8 Review of Safety

Safety Review Approach

The sponsor did not conduct any clinical safety studies in support of this NDA. Instead, the sponsor conducted a BE and a comparative BA study to establish a bridge to the LD, Prevacid[®] 24HR[®] (NDA 022327, Novartis). In addition to these studies, the sponsor is relying on the Agency's findings of safety and efficacy for LD and data identified in the published literature, to

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

support approval of the TD. The safety of TD is supported by the studies conducted in support of the approval of LD, including three clinical studies identified in the published literature that were conducted to demonstrate the efficacy of LD to treat frequent heartburn over a 14-day course in adults 18 years of age or older. To support the safety of the excipients in DPT's formulation and the 14-day dosing of the TD, a justification was provided in electronic submission located in M2.6.6.

The sponsor also references the Integrated Summary of Safety (ISS) submitted in the NDA for the cumulative time period of 2008 to 2014 and the 120-day Safety Update through September 15, 2015. One new safety signal related to PPIs, a low risk for SCLE, was identified from the analysis of updated search data. Overall, the results of the 120-day Safety Update were consistent with prior safety data reported in the NDA submission. According to DPT, the ISS included worldwide post-marketing data from the global marketing of LD and evaluation of specific safety topics, worldwide literature review, and data from external global safety databases.

The postmarketing data from the FAERS, WHO, NPDS, and DAWN databases are discussed in detail in the latter part of this section.

Lansoprazole was approved in the USA for adults in May 1995 as Prevacid[®], children one to 11 years of age in 2002, and for adolescents 12 to 17 years of age in 2004. Consumers have safely self-treated heartburn with OTC PPIs when omeprazole (Prilosec[®] OTC) was approved to treat frequent heartburn in June 2003 and the LD was approved in May 2009. The safety and efficacy of LD is well established for both, the Rx and OTC use.

The PPIs are generally well tolerated and the AEs are generally mild and reversible in nature. The most common AEs of Prevacid[®] 24HR are diarrhea, headache, constipation, and vitamin B12 deficiency (long-term use). The DFL for Prevacid[®] 24HR has the following warnings:

- Ask a doctor before use if you have:
 - Liver disease
 - Had heartburn over 3 months. This may be a sign of a more serious condition.
 - Heartburn with lightheadedness, sweating or dizziness
 - Chest pain or shoulder pain with shortness of breath, sweating, pain spreading to arms, neck, or shoulders; or lightheadedness
 - Frequent chest pain
 - Frequent wheezing, particularly with heartburn
 - Unexplained weight loss
 - Nausea or vomiting
 - Stomach pain

- Ask a doctor or pharmacist before use if you are taking:

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

- Warfarin (blood-thinning medicine)
 - Prescription antifungal or anti-yeast medicines
 - Digoxin (heart medicine)
 - Theophylline (asthma medicine)
 - Tacrolimus or mycophenolate mofetil (immune system medicines)
 - Atazanavir (medicine for HIV infection)
 - Methotrexate (arthritis medication)
- Stop use and ask a doctor if:
 - Your heartburn continues or worsens
 - You need to take this product for more than 14 days
 - You need to take more than 1 course of treatment every 4 months
 - You get diarrhea
 - If pregnant or breast-feeding, ask a health professional before use
 - Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Many of the above safety concerns are associated with long term use. As the indication for the TD is for a 14-day treatment period, these safety concerns are of a less concern for OTC consumers.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Novartis submitted three published clinical trials which involved a total of 1986 patients for the treatment of frequent heartburn to support approval of Prevacid[®] 24HR (NDA 022327). The sponsor is relying on these same trials to support the safety of its product for the treatment of frequent heartburn. According to the sponsor, the breakdown of these studies showed 861 patients received lansoprazole 15 mg, 277 received lansoprazole 30 mg, and 848 patients received placebo for 14 consecutive days (Kushner, 2009; Peura, 2009b). All subjects had a history of frequent heartburn occurring ≥ 2 days per week over the past month. There were approximately twice as many women enrolled in each treatment group as men. According to the sponsor, approximately 70% of the enrolled population was Caucasian, with the remainder of the study population being Hispanic and African American. Demographic information from the 3 pivotal studies conducted for the approval of the LD on which the sponsor intends to rely on for approval of the TD is provided in Table 8.

Table 8: Demographic data across populations of pivotal studies in support of the approval of Prevacid® 24HR

	Peura 2009		Kushner 2009 Study 1		Kushner 2009 Study 2		
	Lansoprazole 15 mg (n = 291)	Placebo (n = 284)	Lansoprazole 30 mg (n = 277)	Lansoprazole 15 mg (n = 282)	Placebo (n = 282)	Lansoprazole 15 mg (n = 288)	Placebo (n = 282)
Gender – N(%)							
Male	118 (40.5)	101 (35.6)	99 (34.6)	104 (36.9)	100 (35.5)	98 (34.0)	92 (32.6)
Female	173 (59.5)	183 (64.4)	181 (65.3)	178 (63.1)	182 (64.5)	190 (66.0)	190 (67.4)
Race – N(%)							
Caucasian	196 (67.4)	191 (69.0)	183 (64.4)	195 (69.1)	195 (69.1)	218 (75.7)	209 (74.1)
Black Asian	39 (13.4)	41 (14.8)	38 (13.4)	26 (9.2)	30 (10.6)	32 (11.1)	32 (11.3)
Hispanic	10 (3.4)	9 (3.2)	12 (4.2)	11 (3.9)	9 (3.2)	1 (0.3)	1 (0.4)
Other	44 (15.1)	35 (12.6)	45 (15.8)	39 (13.8)	39 (13.8)	34 (11.8)	39 (13.8)
	1 (0.4)	6 (2.1)	6 (2.1)	11 (3.9)	9 (3.2)	3 (1.0)	1 (0.4)
Age (years)							
Mean ± SD	48.2 ± 14.5	48.8 ± 14.1	47.4 ± 13.7	46.3 ± 13.8	48.1 ± 13.8	49.5 ± 14.1	47.6 ± 13.2
BMI (kg/m ²)							
Mean ± SD	30.5 ± 7.4	29.9 ± 6.7	30.8 ± 7.5	30.0 ± 7.1	30.0 ± 7.0	30.5 ± 7.3	30.4 ± 6.9

BMI = Body Mass Index; SD = standard deviation

[Source: modified from the sponsor's submission, Table 4, p. 19 of 114, M5.3.5.3]

According to the sponsor, the age range of the patients in the clinical studies conducted for the approval of the LD extended from neonates to geriatrics. No reports of difference in PK between geriatric patients and adults or differences between men and women were observed. In the pediatric population of one month to one year of age, the LD Rx was ineffective for the treatment of symptomatic GERD in a multicenter, double-blind, placebo-controlled study.

According to the sponsor, the approved the LD Rx formulation was studied in more than 10,000 patients in Phase 2 or Phase 3 clinical trials involving various doses and durations of treatment. Distribution data for the LD was not provided by the sponsor since it did not obtain the right to this information. The sponsor is relying on the information available in NDA 022327 (Prevacid® 24HR).

8.2.2. Relevant characteristics of the safety population

No safety studies were conducted with DPT's TD since the sponsor is relying on the safety data of the LD. However, the TD was administered to healthy adult volunteers in a BE study in a fasting state and a comparative BA study with and without fasting. A total of 90 subjects were exposed to the TD (72 subjects in Project 120383; 18 subjects in Project 120384), with a single day dosing regimen of 15 mg lansoprazole under fed and fasted conditions and administration with and without water. Both, the TD with and without water as well as LD were well tolerated with no unexpected safety findings. No deaths were reported in the BE and BA studies.

Demographic information from DPT's two pharmacokinetic studies is presented below in Table 9.

Table 9: Table of Baseline Demographic Characteristics for Subjects Stratified by Treatment Arm

Demographic Profile for Combined Study Populations						
Category		Treatment A N=87	Treatment B N=69	Treatment C N=64	Treatment D N=69	Treatment E N=17
Age (years)	Mean ± SD	44±14	44±14	44±14	43±14	48±12
	Range	18-75	18-75	20-75	18-75	25-70
	Median	45	47	47	45	46
Age Groups	<18	0	0	0	0	0
	18-40	36 (41.4%)	28 (40.6%)	26 (40.6%)	30 (43.5%)	5 (29.4%)
	41-64	45 (51.7%)	37 (53.6%)	34 (53.1%)	35 (50.7%)	10 (58.8%)
	65-75	6 (6.9%)	4 (5.8%)	4 (6.3%)	4 (5.8%)	2 (11.8%)
	>75	0	0	0	0	0
Gender	Male	52 (59.8%)	39 (56.5%)	36 (56.3%)	40 (58.0%)	12 (70.6%)
	Female	35 (40.2%)	30 (43.5%)	28 (43.8%)	29 (42.0%)	5 (29.4%)
Race	Asian	0	0	0	0	0
	Black/African American	2 (2.3%)	2 (2.9%)	2 (3.1%)	2 (2.9%)	0
	White	85 (97.7%)	67 (97.1%)	62 (96.9%)	67 (97.1%)	17 (100%)
	Other	0	0	0	0	0
Ethnicity	Not Hispanic	83 (95.4%)	66 (95.7%)	62 (96.9%)	66 (95.7%)	16 (94.1%)
	Hispanic	4 (4.6%)	3 (4.3%)	2 (3/1%)	3 (4.3%)	1 (5.9%)
BMI (kg/m ²)	Mean ± SD	25.20±2.59	25.14±2.68	25.18±2.69	25.06±2.67	25.74±2.16
	Range	19.02-29.52	19.02-29.43	19.02-29.43	19.02-29.43	21.20-29.52
	Median	25.48	25.53	25.52	25.48	25.48
Height (cm)	Mean ± SD	167.5 ± 9.1	167.5 ± 9.0	167.4 ± 9.1	167.4 ± 8.8	168.4 ± 10.1
	Range	148.5 - 190.0	151.5 - 185.0	151.5 - 185.0	151.5 - 185.0	148.5 - 190.0
	Median	167.0	167.0	166.8	167.0	169.5
Weight (kg)	Mean ± SD	71.01 ± 11.31	70.85 ± 11.83	70.93 ± 11.99	70.58 ± 11.57	73.12 ± 9.86
	Range	49.30 - 100.10	49.30 - 100.10	49.30 - 100.10	49.30 - 100.10	54.60 - 88.30
	Median	70.70	69.20	68.75	68.90	73.70

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

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

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).

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

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: modified from the sponsor's submission, Table 5, p. 21 of 114, M5.3.5.3]

8.2.3. Adequacy of the safety database

The PK studies were designed so that subjects received five treatments: lansoprazole 15 mg ODT (TD), fed and fasted, with and without water and Prevacid 24HR[®] (LD) under fasting condition with water. Seventy-seven subjects completed all five treatment periods of the study and 13 subjects discontinued from the study.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The sponsor provided safety data in appropriate format in the appropriate section. The sponsor provided case report forms for subjects who discontinued participation in the PK studies. Appropriate explanations were provided for subjects who deviated from the protocol. The CRO performed the PK studies in one location hence there were no site specific data integrity issues. Submission quality was acceptable for review. Submission was provided in electronic Common Technical Document (eCTD) format. The sponsor responded to information requests in a timely manner.

8.3.2. Categorization of Adverse Events

Adverse event coding in the PK studies was performed using the Medical Dictionary for Regulatory Activities (MedDRA) v16.1 preferred term (PT) and system organ class (SOC) system. According to the sponsor, coding was done within the Medical Writing-Data Management Group of iVentiv Health Clinique (iHC) Early Phase (Quebec, Canada) by personnel who are trained in dictionary coding. If a term failed to auto-encode, the term was manually coded and approved in accordance with iHC Early Phase's MedDRA Coding Conventions. Once a term was manually coded and approved, all other identical terms were automatically coded by the system. After all terms were coded, terms underwent both peer review and medical review by the principal investigator. All AEs were collected as well as any changes in laboratory or vital signs that may have constituted an AE. AEs were assessed according to frequency, severity, seriousness and suspected causality. The incidence and the total number of reported AEs were presented for each treatment period and for all treatment periods combined.

8.3.3. Routine Clinical Tests

Subjects enrolled in the PK studies were members of the community at large. Subject screening procedures were performed within 28 days prior to first study drug administration and included informed consent, inclusion/exclusion check, medical history, medications history, a concomitant medication check, demographic data (gender, age, race, and ethnicity), body measurements (height, weight, and body mass index (BMI)), physical examinations, vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature), a 12-lead electrocardiogram (EKG), a urine drug screen, a urine pregnancy test (female subjects), clinical laboratory measurements (biochemistry, hematology, serology [Human Immunodeficiency Virus (HIV), Hepatitis C (HCV) antibodies, and Hepatitis B surface antigen (HBsAg)], and urinalysis). Tobacco consumption was allowed but all subjects were restricted from using tobacco for at least two hours pre-dose and four hours post-dose.

Subjects were confined to the CRO from at least 10 hours prior to drug administration and until after the 12-hour post-dose blood draw, in each period. Each treatment phases were separated by washout periods of seven days.

Upon arrival at the CRO facility for the first confinement, each subject was assigned an enrolment number. A urine drug screen, urine pregnancy screen (all female subjects), and an alcohol breath test were performed for all subjects prior to drug administration in each period. In case of a positive result for urine drug screen, the sample was sent to the Biomedical Laboratory for confirmation analysis. Female subjects of childbearing potential and who had sexual intercourse with a non-sterile male partner were advised to use an acceptable method of contraception for 30 days prior to study drug administration and until 30 days following the last drug administration. Acceptable methods of contraception are listed in the submission on page 21 of Project 120383 in the submission.

A safety assessment of the oropharyngeal area was performed on each subject before, shortly after study drug administration, and just prior to discharge from each study period.

Throughout the study, subjects were monitored for AEs. At the time of admission and departure, subjects were asked standard probing questions concerning the onset of any new health problems. All AEs, including those reported within three days following last drug administration were recorded.

Study exit procedures were performed for all subjects whether they did or did not complete the study. Study exit procedures included clinical laboratory tests and EKG evaluation to confirm the absence of significant changes in each subjects' state of health.

8.4. Safety Results

Deaths

There were no deaths in either of the PK studies.

8.4.2. Serious Adverse Events

There were no serious adverse events reported in either of the PK studies.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Twelve subjects discontinued study participation. Eight subjects withdrew for personal reasons without further information in the narratives. Three out of eight patients returned to participate in the latter stages of the PK studies. One subject withdrew due to poor vein assessment for blood draw. One subject withdrew due to difficulty with blood collection. Another subject withdrew due to dizziness after a blood draw. Subject 47 had a serious adverse event that was unrelated to the TD. Subject 47 became pregnant despite using a condom with spermicide. Subject 47 received the LD 25 days before she found out that she was pregnant. Subject 47 terminated her pregnancy which was labeled as serious AE.

8.4.4. Significant Adverse Events

As noted above, subject 47 had a serious adverse event that was unrelated to the TD. Subject 47 became pregnant despite using a condom with spermicide. Subject 47 received the LD 25 days before she found out that she was pregnant. Subject 47 terminated her pregnancy which was labeled as serious AE. No other significant AEs were reported in the PK studies.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

As per sponsor's protocol, Treatment Emergent Adverse Event (TEAE) is an AE that began on or after the first study drug administration or an AE that began before the first study drug administration and worsened in severity after study drug administration or may have been prolonged due to administration of the study drug. In the case of a TEAE with an onset time during the washout period or just prior to the next study drug administration, it was attributed to the study drug taken during the previous treatment period.

In Project 120384, there were a total of five TEAEs reported by three of the 18 subjects who received at least one dose of the TD. No TEAEs were reported in group A and five TEAEs were reported in group B as outlined in Table 10.

Clinical Review
 Ketan P. Parikh, M.D.
 NDA 208025 / SN 0004
 Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Table 10: Frequency of subjects experiencing TEAEs summarized by treatment

System Organ Class	Treatment Group	
	A	B
MedDRA® Preferred Term		
Number of subjects dosed	17	18
Gastrointestinal disorders		1(5.6%)
Nausea		1(5.6%)
Nervous system disorders		2(11.1%)
Headache		2(11.1%)
Respiratory, thoracic and mediastinal disorders		1(5.6%)
Dyspnea		1(5.6%)
Vascular disorders		1(5.6%)
Hot flush		1(5.6%)
Total	0 (0.0%)	3 (16.7%)
MedDRA®: Medical Dictionary for Regulatory Activities.		

Test (A) = Dexcel Pharma Technologies Ltd., Israel, Lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet (fed condition).

Test (B) = Dexcel Pharma Technologies Ltd., Israel, Lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet (fasting condition).

[Source: Sponsor's submission, Project 120384, Table 14.3.1.1-1, page 96/102]

In Project 120383, the sponsor reported a total of 56 TEAEs by 28 of the 72 subjects. The most commonly reported TEAEs were headache by 16.7%, nausea by 6.9%, and dizziness by 5.6% of the subjects. Please see Table 11 for summary of TEAEs.

Clinical Review
 Ketan P. Parikh, M.D.
 NDA 208025 / SN 0004
 Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Table 11: Frequency of subjects experiencing TEAEs summarized by treatment

System Organ Class MedDRA® Preferred Term	Treatment Group			
	A	B	C	D
Number of subjects dosed	69	69	64	69
Ear and labyrinth disorders	1 (1.4%)			
Ear pain	1 (1.4%)			
Gastrointestinal disorders	1 (1.4%)	4 (5.8%)	2 (3.1%)	6 (8.7%)
Abdominal pain				1 (1.4%)
Gingival inflammation				1 (1.4%)
Nausea		1 (1.4%)	1 (1.6%)	3 (4.3%)
Stomatitis		2 (2.9%)	1 (1.6%)	
Tongue disorder	1 (1.4%)	1 (1.4%)		1 (1.4%)
General disorders and administration site conditions		2 (2.9%)		1 (1.4%)
Asthenia		1 (1.4%)		1 (1.4%)
Fatigue		1 (1.4%)		
Infections and infestations				1 (1.4%)
Gastroenteritis				1 (1.4%)
Injury, poisoning and procedural complications	2 (2.9%)			2 (2.9%)
Post procedural discomfort	2 (2.9%)			1 (1.4%)
Procedural dizziness	1 (1.4%)			1 (1.4%)
Musculoskeletal and connective tissue disorders			1 (1.6%)	
Back pain			1 (1.6%)	
Nervous system disorders	5 (7.2%)	3 (4.3%)	7 (10.9%)	8 (11.6%)
Dizziness		1 (1.4%)	2 (3.1%)	1 (1.4%)
Headache	4 (5.8%)		6 (9.4%)	5 (7.2%)
Somnolence	1 (1.4%)	2 (2.9%)	1 (1.6%)	2 (2.9%)
Respiratory, thoracic and mediastinal disorders	1 (1.4%)	2 (2.9%)	1 (1.6%)	1 (1.4%)
Cough		1 (1.4%)		
Nasal congestion	1 (1.4%)	1 (1.4%)	1 (1.6%)	
Oropharyngeal pain				1 (1.4%)
System Organ Class MedDRA® Preferred Term	Treatment Group			
Number of subjects dosed	A	B	C	D
	69	69	64	69
Vascular disorders	1 (1.4%)			
Hot flush	1 (1.4%)			
Total	10 (14.5%)	9 (13.0%)	9 (14.1%)	13 (18.8%)

MedDRA®: Medical Dictionary for Regulatory Activities.

Test-1 (A) = Dexcel Pharma Technologies Ltd., Israel, lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, allowed to disintegrate for 60 seconds and swallowed without water.

Test-2 (B) = Dexcel Pharma Technologies Ltd., Israel, lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, allowed to disintegrate for 60 seconds and swallowed with water.

Test-3 (C) = Dexcel Pharma Technologies Ltd., Israel, lansoprazole 1 x 15 mg delayed-release orally disintegrating tablet, swallowed with water.

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

[Source: Sponsor's submission, Project 120383, Table 14.3.1.1-1, page 202/212]

8.4.6. **Laboratory Findings**

Clinical laboratory evaluations were performed at screening and study exit. Clinically significant laboratory changes were defined as those who fall outside the acceptable range which was predefined in the guide of Biomedical Laboratory Reference and Acceptable Ranges. An abnormal repeat value was reviewed by a qualified investigator or sub-investigator to assess whether or not the value had meaningfully changed from the baseline. If it was determined to be a clinically meaningful change, an AE was opened.

In the Project 120383, some subjects had study exit laboratory results that were repeated in order to confirm the initial out-of-range results. All of these results were within normal limits or were judged to be not clinically significant by a Medical Sub-Investigator. Pregnancy tests were negative for all female subjects over the course of the study, with the exception of Subject 47 during Period 3 despite adequate birth control measures.

In Project 120384, all final laboratory results were within normal limits or were judged to be not clinically significant by a Medical Sub-Investigator according to the sponsor. Study exit hematology analysis was not performed on one subject (Subject 3) due to blood sample clotting and the subject declined repeat blood draw. The Medical Sub-Investigator reported that the number of test drug samples that were administered is unlikely to have any significant clinical safety concern. Pregnancy tests were negative for all female subjects over the course of the study.

The sponsor submitted all of the laboratory test result values.

8.4.7. **Vital Signs**

Vital signs were measured at the time of screening only. The sponsor submitted vital signs summary descriptive statistics table which showed that the baseline vital signs were within normal range.

8.4.8. **Electrocardiograms (ECGs)**

The sponsor states that ECGs were performed at the time of screening and upon study exit. Electrocardiograms Summary Descriptive Statistics and Change from Screening to Study Exit Table was reviewed. The mean change between baseline and study exit parameter of heart rate was 5.2 beats per minute, PR interval was -2.3 milliseconds (ms), QRS interval was -1.0 ms, QT interval was -15.9 ms, and QTc interval was 0.1 ms. The mean changes in parameters listed above were considered insignificant by the Investigators and the sponsor. This reviewer agrees with that assessment.

8.4.9. QT

The sponsor reported baseline and study exit ECG findings. The QT and QTc intervals remained within normal limits during the PK studies. Mean QT and QTc changes are outlined in Section 8.4.8 of this review.

8.4.10. Immunogenicity

Not applicable to this study.

8.5. Analysis of Submission-Specific Safety Issues

The sponsor was required to submit oropharyngeal assessment of all subjects enrolled in the PK studies due to the orally disintegrating drug delivery technology. According to the sponsor, the oropharyngeal area assessments were performed by certified physicians and registered nurses who were qualified to perform this type of assessments. The oropharyngeal assessments were performed as per the study protocol; screening, prior to dosing, shortly after dosing, and 12 hours post-dose, all utilizing the same process. The medical staff performed oropharyngeal assessments looking for any signs of erythema, irritation, edema, vesicles, ulcers, or any other particularities in the buccal cavity which includes the interior of cheeks and gums, the upper and lower mouth surfaces, behind the rear teeth, upper and under the subject's tongue, and at the oropharyngeal cavity. Any observation noted at the time of the oropharyngeal assessments were documented, and post-study assessments were compared to the oropharyngeal assessments baseline observation.

Severity of the oropharyngeal observations were determined by the physician or the registered nurse who performed the oropharyngeal assessment. The determination of the severity level was done per the following description:

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]

Only clinically significant observations led to the reporting of an AE, and had a follow-up performed until the AE resolved. The severity of the oropharyngeal assessment was reviewed by the Principle Investigator according to their medical judgment and experience. The severity of the oropharyngeal assessment was performed at the time of the relationship assessment.

8.5.1. Oropharyngeal Assessments

The sponsor submitted transport files containing the results of the oropharyngeal assessments for the PK studies. In summary, no significant abnormalities were reported by the sponsor. In Project 120383, subject 43 withdrew after dosing in the second period due to difficulties with blood draw. Shortly after the drug administration, no abnormalities were detected and suddenly the subject decided to leave the clinic prematurely, and the oropharyngeal area evaluation was not conducted before the departure. The sponsor performed a telephone follow-up on the next day. The subject did not report any redness, pimple, or wound in the mouth.

A total of 90 subjects participated in the oropharyngeal evaluation. A total of 308 evaluations were performed. Oropharyngeal findings were found in 14 out of the 308 evaluations: 11 findings described in six subjects were considered unrelated since they were also present before dosing. Three findings (light redness on tongue) were considered possibly related and were noted in subject 18 (received the LD) and in subjects 36 and 33 (received the TD). Slight redness was also noticed in subject 36 in prior period before dosing. In all three cases, the redness was classified as mild and it spontaneously resolved. No oropharyngeal findings were found when the patients were discharged.

No oropharyngeal findings were observed in Project 120384.

8.6. Specific Safety Studies/Clinical Trials

As noted in Section 8.5, the sponsor conducted oropharyngeal studies to assess the safety of lansoprazole ODT due to its orally disintegrating drug delivery technology. Refer to Section 8.5 for further details.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

No carcinogenicity studies were performed for this NDA. Carcinogenicity is not expected with proposed limited use of lansoprazole ODT (b) (4) mg in the OTC setting.

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

The sponsor did provide published genotoxicity and carcinogenicity data of lansoprazole to support its safety for limited use.

According to the sponsor, 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 (UDS) test, the in vivo mouse micronucleus test, or the rat bone marrow cell chromosomal aberration test.

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated with oral lansoprazole at doses of 5 to 150 mg/kg/day, which is 1 to 40 times the exposure, on a body surface area (BSA) basis of 50-kg person of average height. Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in the male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium 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 (4 to 40 times the recommended human dose, based on BSA) exceeded the low background incidence (range = 1.4% to 10%) for this strain of rat. Similarly, CD-1 mice treated with 2-80 times the recommended human dose based on BSA produced dose-related increased incidence of gastric ECL cell hyperplasia and hepatocellular adenoma plus carcinoma. Male mice receiving 10-80 times the human dose were found to have increased incidence of adenoma of rete testis.

According to the sponsor, a 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive. In a long-term study of high-dose PPI administration in *Helicobacter pylori* infected Mongolian gerbils, lansoprazole was found to enhance neuroendocrine tumor development in the glandular stomach. No stomach cancers developed, however, the development of atrophic gastritis in *Helicobacter pylori* positive patients treated with long-term PPIs could potentially be of concern.

8.7.2. Human Reproduction and Pregnancy

There were no reproductive or pregnancy studies conducted for this NDA. The sponsor submitted animal data of lansoprazole.

The sponsor is relying on safety data of listed drug, Prevacid[®] 24HR OTC (NDA 022327, Novartis). According to the sponsor, Prevacid[®] 24HR OTC was approved via 505 (b)(1) pathway. Novartis, owner of the NDA 022327, did not conduct any pregnancy or non-clinical studies; instead Novartis relied on the data generated in the original application for Prevacid[®] Rx Capsules (NDA 020406) by Takeda once Novartis was granted full rights of reference to the data by Takeda.

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

According to the sponsor, lansoprazole at oral doses up to 150 mg/kg/day was found to have no effect on male or female rat fertility and reproduction. In a study in chicks, developing embryos were administered lansoprazole for 5 days; this treatment completely inhibited mineralization of all leg and wing long bones which is likely related to inhibition of PHOSPHO1, a bone-specific phosphatase that been implicated in the initiation of inorganic phosphate generation for matrix mineralization. In the 5-week old mice, lansoprazole injections for 8 weeks led to enhanced aquaporin-4 and KCNQ1 gene expression which leads to unbalanced water flow by the gastric mucosa due to loss of gastric juice volume from PPIs. In addition, overexpression of aquaporin-4 and KCNQ1 impairs parietal cell and mucous neck-to-zymogenic cell differentiation which may be responsible for the development of gastric fundic gland polyps in the stomach with long-term PPIs use.

According to the sponsor, lansoprazole and its metabolites are secreted in the milk of rats but it is unknown whether lansoprazole is excreted in human milk. Many drugs are excreted in human milk, because of potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of heartburn relief in a nursing mother. The proposed DFL advises nursing women to ask a doctor before they use lansoprazole.

Clinical review of Prevacid[®] 24HR OTC (NDA 022327) by Lolita A. Lopez, MD submitted in DARRTS on 03/16/2009 states:

Lansoprazole is a pregnancy category B drug, that there are, no adequate or well-controlled studies in pregnant women, and that lansoprazole should be used during pregnancy only if clearly needed.

Pregnancy-related reports during postmarketing:

From the sponsor's postmarketing data, there were 114 cases identified that are related to drug exposure to lansoprazole during pregnancy. More than half (55%, 63/114) of the cases either had no reported adverse effects or no fetal outcome reported. The following is a breakdown of half of the cases: 12 congenital anomalies resulting in live births, 10 non-serious cases of maternally related AEs only, 9 cases of spontaneous abortion, 8 cases of healthy infants/no abnormalities reported, 4 serious cases with fetal outcome unknown, 2 cases of still births, 2 cases of abortion (unspecified) and 1 case of each: abortion (missed), tubal pregnancy, blighted ovum and intra-uterine death.

The majority of cases had insufficient information to allow meaningful assessment of causality for lansoprazole. In cases where maternal exposure to lansoprazole during pregnancy was followed by the occurrence of a congenital anomaly in the infant, no consistent pattern of abnormalities was suggested. It should be noted that one of every

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

33 babies is born with a birth defect; in the United States, about 3% of babies are born with birth defects (CDC).

Spontaneous abortions occur in about 15% to 20% of all known pregnancies (ACP Medicine Online Chapter VIII). The spontaneous abortion reports during postmarketing did not suggest any untoward incidence that could be reasonably attributed to lansoprazole use alone.

Deaths following drug exposure during pregnancy during postmarketing:

From the sponsor's postmarketing data, there were three cases with reported outcome of fetal deaths:

- THQ2001A02326: exposure in utero to lansoprazole with fetal death at 21 weeks of pregnancy. No further information provided
- TPG2002A00124: exposure in utero to lansoprazole with spontaneous abortion at seven weeks of pregnancy
- THQ2003A00291: a case of a single dose of lansoprazole use in a pregnant woman; ultrasound showed a hydrocephalic fetus (dosage strength not provided). Spontaneous abortion occurred at nine weeks. No further information provided.

Medical Literature and Pregnancy

It is concluded in two publications that PPIs do not present a major teratogenic risk in humans when used at recommended doses. One study (Diav-Citrin, 2005) published in 2005 was a multicenter prospective controlled cohort study conducted within the European Network of Teratology Information Services. The authors followed a total of 410 pregnancies exposed to omeprazole (total of 295 with 233 in the first trimester), lansoprazole (total 62, 55 in first trimester) and pantoprazole (total 53, 47 in first trimester). Results showed that the rate of major congenital anomalies did not differ between the exposed and control groups either overall or in the first trimester after exclusion of genetic, cytogenetic or infectious anomalies. Another study (Nikfar, 2002) was a meta-analysis of five published studies in 2002 which analyzed the available data on the risk for malformations following use of PPIs in the first trimester of pregnancy. The authors stated that the majority of exposures in the publications were to omeprazole; however, breakdown the distribution of exposures to PPIs was not provided. A total of 593 infants were exposed to PPIs, most often omeprazole. The summary relative risk for all major malformations was 1.18 (95% CI 0.72- 1.94) among PPI-exposed infants. In addition, the meta-analytic summary incidence rate for major malformations (2.8%; 95% CI 1.8–3.8), was well within the range expected among the general population. These results are consistent with the animal data as well as with the available human case reports.

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Medical officer comments:

The information provided on pregnancy does not preclude use of lansoprazole ODT nor warrant changes in the current DFL. The risks associated with lansoprazole use in pregnant or nursing mothers have not been formally investigated clinically; therefore, this drug should be used only if needed. The proposed label appropriately directs pregnant or nursing mothers to consult a health care provider before use; this is consistent with current language on the RD, Prevacid[®] 24HR.

8.7.3. Pediatrics and Assessment of Effects on Growth

No information was provided by the sponsor.

Medical officer comments:

The sponsor submitted an Initial Pediatric Study Plan (iPSP) dated February 28, 2014 for lansoprazole ODT to Pre-Investigational New Drug application 118528. The Agency received the iPSP on March 4, 2014. The sponsor confirmed receipt of the Agency's comments to the iPSP on June 2, 2014. 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.

Treatment of heartburn in the pediatric population with OTC Lansoprazole ODT is inappropriate since pediatric gastroenterologists recommend that children with symptoms of heartburn should be under the care of a physician. The agency's current position is that the treatment of heartburn in the pediatric population is not appropriate in the OTC setting and a physician should be consulted before use of PPIs in children under 18 years of age. This is consistent with the OTC PPI products currently approved and marketed in the USA (i.e., omeprazole and esomeprazole).

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reports of overdose, drug abuse, or dependency in the PK studies.

The sponsor held marketing agreements in the UK and in Germany from 2006-2013. According to the sponsor, marketing agreements were withdrawn in both countries due to marketing considerations. Periodic Safety Update Reports (PSUR) from November 2006 to March 2011 revealed 56 cases of adverse drug reactions and none of them were confirmed to be associated with DPT's product. Pharmacovigilance was terminated in December 2013 during which time the sponsor noted total of 96 cases of adverse drug reactions and only one case was confirmed to be associated with DPT's product. The case involved a 57-year-old female (20120981 ID/ISR)

who administered 15 mg lansoprazole and experienced dyspnea, erythema, pruritus and blood pressure increase.

According to the sponsor, lansoprazole is not dialysable from circulation by hemodialysis. The sponsor reports that most of the overdose cases reported for lansoprazole resulted in no effect and none were classified as a major effect. There were only three cases with moderate effect: a 2-year-old male accidentally administered a 300 mg dose, a 70-year-old female who attempted suicide deliberately administered 450 mg dose, and a 3-year-old female accidentally administered a 900 mg dose. There were a total of 97 case reports of overdose for lansoprazole as reported to the American Association of Poison Control Centers between the years of 2008 to 2014.

The sponsor evaluated and submitted drug abuse data from DAWN. The data covered periods 2004-2011 (most recent data available). The data from DAWN does not separate individual PPIs hence; it is difficult to assess the potential for abuse. Despite the inability to separate out data regarding individual PPIs, the data suggests very limited emergency department visits for PPIs abuse. According to the sponsor, many of the cells in the data table show the symbol “*” in the absence of a numerical value. The symbol “*” represents that the number did not meet the DAWN Standards for precision either because the standard error was too large, or the estimate was below 30. There were no clear safety signals suggestive of abuse risk or misuse with PPIs, or more specifically lansoprazole.

According to the sponsor, no specific information is available on withdrawal and rebound effects of lansoprazole.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

The sponsor submitted this NDA in August 2015 with postmarketing safety data as well as 120-day Safety Update in December 2015. The sponsor did not conduct any clinical safety studies in support of this application. Rather, the sponsor is relying on the Agency’s findings of safety and efficacy for LD (Prevacid[®] 24HR, NDA 022327, Novartis). The sponsor states that the LD is currently approved and marketed in over 92 countries including the USA, UK, Japan, and Europe. The sponsor reports that the prescription strength Prevacid[®] (NDA 020406, Takeda) has been approved in the USA for over 21 years and used internationally for almost 30 years with excellent track of safety. The approved Prevacid[®] Rx labeling states that over 10,000 patients have been treated with Prevacid[®] in Phase 2 or Phase 3 clinical trials involving various doses and duration of treatment.

According to the annual report of Prevacid[®] 24HR (NDA 022327), over (b) (4) doses were

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

sold from May 18, 2014 to May 17, 2015 in the USA. The annual distribution of Prevacid[®] Rx was between May 10, 2014 to May 9, 2015 was over [REDACTED] (b) (4) doses in the USA.

Adverse events reported in the postmarketing databases are most often mild and reversible in nature. The safety profile is similar for different formulations, treatment groups, and indications. According to the sponsor, there have been no market withdrawals for either safety or regulatory reasons.

As noted above, the sponsor submitted 120-day Safety Update as well as an updated literature review. The sponsor references Prevacid[®] 24HR (NDA 022327) for efficacy and safety. The sponsor included a summary of lansoprazole safety information from five databases (the sponsor's post-marketing database, FAERS, DAWN, NPDS, and WHO).

According to the sponsor, Prevacid[®] Rx (NDA 020406) has a well-established safety profile and has been marketed for prescription use for over two decades. Prevacid[®] Rx was first approved on May 10, 1995 in the USA followed by Prevacid[®] 24HR OTC which was approved on May 18, 2009 in the USA.

The sponsor's submission includes post-marketing data from NPDS, FAERS, WHO, DAWN, and literature search. A 120-day Safety Update was submitted in December 2015.

Overall, the safety narrative is consistent in the databases and literature. Lansoprazole is well tolerated drug product with most of the AEs that are infrequent and minor to mild in nature. Most of the safety signals identified in the databases are related to higher doses of lansoprazole and longer in duration than the sponsor's proposed drug product. The four postmarketing databases that were analyzed include the FAERS, DAWN, NPDS, and WHO. All databases were searched back to 2008 through the most recently available data. According to the sponsor, FAERS identified many AEs related to lansoprazole use, but only nine events reported in four patients were related to the LD. The data from DAWN and NPDS databases are similar in that lansoprazole is typically not a drug of abuse hence; misuse is what is generally captured in the DAWN database. The majority of the events reported fell into one of three categories: no effect; not followed, judged as nontoxic exposure (clinical effects not expected); not followed, minimal clinical effect possible (no more than minor effect possible), which supports the safety of lansoprazole.

The 120-day Safety Update in the WHO database search identified a new safety signal which is a low risk safety signal for SCLE. Recent data suggests that PPIs are associated with infrequent cases of SCLE, but the exact risk cannot be estimated due to the low incidence rates. The prescribing information for OTC PPI products in Europe were revised to warn of this risk as of July 2015. The Agency is currently evaluating potential SCLE risk and has issued a Tracked Safety Information request.

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

National Poison Data System (NPDS)

The American Association of Poison Control Centers (AAPCC) maintains the national database of information logged by the country's 57 poison control centers. Exposures do not necessarily represent a poisoning or an overdose. The AAPCC is not able to completely verify the accuracy of every report made to their member centers. According to the sponsor, the marketing status (Rx versus OTC) was not provided in the database. Between 2008 and 2015 (including 120-day Safety Update), the total number of events were 13,066. More females than males reported poisoning incidents (53.5% vs. 46.5%). 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). Many OTC PPIs are not approved for use in a pediatric population so it is possible that many of the reported events were accidental exposures and not related to indicated usage of the drug product. The sponsor will not be marketing the proposed drug product to the pediatric population. In addition, the sponsor will be packaging the TD in a child resistance container closure, hence; the risk for poisoning events in pediatric population should be reduced. The most frequently reported poisoning doses were 1 or 2 tablets, but the actual amount of PPI could not be ascertained. The number of poisoning events decreased as the dose increased. For example, there were a total of 4,626 events with 1-2 doses compared to 183 and 108 events with 10 and 15 doses respectively. There were a total of 3 deaths, 78 major effect, 385 moderate effect, 742 minor, and the majority (3,209) had no effect. The NPDS data suggests fewer poisoning events with shorter duration of use as proposed by the sponsor. For example, the NPDS data from 2008 to 2015 showed that the number of poisoning events with > 3 months use was 1,723 compared to more than one week but less than one month of use which showed 303 events. The total number of events reported to the NPDS database from 2008 to 2015 decreased yearly in a linear fashion (2008: 2,577, 2014: 1,031, and until September of 2015: 687).

Food and Drug Administration Adverse Events Reporting System (FAERS)

According to the sponsor, the FAERS database contains extensive amount of AEs data associated with lansoprazole use and many are duplicate cases. The sponsor provided data that reflects cases where lansoprazole was the primary suspect in the AE from 2008 to second quarter of 2015 (includes 120-day Safety Update). The sponsor removed data if the same unique subject was coded with multiple same events, indication(s), and outcome code. Cases pertaining to other PPIs were also removed.

A total of 3,528 events were reported in 1,006 subjects during the period 2008 to second quarter of 2015. According to the sponsor, analysis of these events led to their conclusion that the majority of the AEs were associated with higher dosing and longer duration of lansoprazole Rx product than the proposed DPT lansoprazole OTC drug product. According to the sponsor, the LD, Prevacid[®] 24HR (NDA 022327) was listed only nine times in the FAERS database during the timeframe examined (2008 to second quarter 2015). The main difference between the LD

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

and TD is that the LD is a capsule filled with pellets and the TD is an orally disintegrating tablet. The sponsor's analysis of the reported events per formulation revealed no increase in AEs in the ODT formulation compared to the capsule formulation. Moreover, none of the AEs preferred terms that occurred in the more than 15 unique patients were AEs related to the mouth, which is a potential safety concern with the sponsor's proposed product. The FAERS data suggests more females reported lansoprazole-related AEs in comparison to males. Data also suggests that individuals over the age of 40 reported more events than individuals under the age of 40. Currently, lansoprazole is approved in 15 mg and 30 mg doses. More AEs were reported with the higher dose than the lower dose. Data also suggests longer duration of use signifies higher frequency of AEs. The sponsor states that the proposed product is for shorter duration and lowest approved dose which should significantly reduce the incidence of AEs. The FAERS outcome data was analyzed by the sponsor. The sponsor reports that many individuals with outcome codes that included death, hospitalization, or life-threatening AEs were present in individuals with serious health maladies and these individuals were taking lansoprazole to remedy secondary health issues. In addition, the numbers of AEs reported for ODT formulation are fewer than the LD capsules with no events reported for ODT lansoprazole in the four most recent quarters of FAERS data. The FAERS database reported one subject having 7 events in congenital abnormality outcome section but it is unclear which ODT PPI was associated with these outcomes.

According to the sponsor, 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 FAERS database also had numerous reports of drug ineffectiveness.

According to the sponsor, one potential safety concern with its product is the orally disintegrating technology, however; there were no mouth-related AEs recorded on the FAERS database list suggesting a low risk of lansoprazole ODT causing local drug effects in the mouth. The 120-day Safety Update confirmed 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) suggesting that there is no increased risk for any specific AEs for the ODT product. The sponsor provided FAERS database reports on all currently available formulations of lansoprazole. The sponsor reports that there is a large variability in the number of AEs reported by different formulations, however; 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 of TD for 14-day course.

World Health Organization (WHO)

The sponsor performed a search in the WHO publications database for lansoprazole covering

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

2008 to May 2015 and the 120-day Safety Update covered the time period of May 2015 through September 2015. According to the sponsor, the search revealed a list of publications which present several known safety issues associated with lansoprazole and PPIs in general with 10 cases where lansoprazole was administered as a concomitant drug and was not associated with AEs. Majority of the reports were already evaluated by the Agency and led to a class labeling change in PPIs. According to the sponsor, 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.

The 120-day Safety Update revealed a new signal of a low risk magnitude for SCLE with PPIs use. Both, the EMA and MHRA required OTC and Rx PPIs labeling change in July 2015 and August 2015 respectively. As noted above, the Agency is tracking this safety issue, however; the Agency has not issued a safety warning in regards to SCLE.

There were 10 cases reported in which lansoprazole was administered as a concomitant treatment but it did not pose any safety issues according to the sponsor, since, lansoprazole was not the suspected drug in any of the cases. The sponsor retrieved these cases along with details from the WHO regarding suspected drug, events, and other concomitant drugs. The sponsor subsequently assessed whether the drug interaction between lansoprazole and the suspected drug is listed in the approved labeling of both Rx and OTC lansoprazole products. The sponsor found that lansoprazole is only mentioned as a concomitant drug in all AEs reports, in no case is lansoprazole listed as the suspected drug product.

Medical officer comment:

The summary of 10 reported cases were reviewed by this medical officer. It does not appear that any one of the 10 case reports are secondary to lansoprazole use but rather that it was administered concomitantly with the suspected drug(s).

Proton Pump Inhibitors and Atazanavir

According to the sponsor, interaction between PPIs and atazanavir is well known and it was published in 2013. Lansoprazole decreased atazanavir AUC by 94% and omeprazole decreased atazanavir (+ ritonavir) AUC by 75%. Co-administration with PPIs is contraindicated for treatment-experienced patients in the Prescribing Information Packet in the United States and not recommended for any patients in the European Summary of Product Characteristics (SmPC). This drug interaction was implemented in the DFL of the LD which was also incorporated in to the DFL of the TD.

Proton Pump Inhibitors and Risk for Fractures

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

The Australian Adverse Drug Reactions Bulletin published three large retrospective studies which suggested an association between PPIs and an increase incidence of fractures in February 2009. The Agency presented its findings in WHO Newsletter Number 4, 2010 confirming an association between PPIs and fractures. On May 25, 2010 which was updated on March 23, 2011, the Agency issued Safety Announcements regarding the risk of bone fractures: "Following a thorough review of available safety data on 6 epidemiologic studies, the FDA has concluded that fracture risk with short-term, low dose PPI use is unlikely." Therefore, the Agency determined that an osteoporosis and fracture warning on the OTC PPI medication DFL is not indicated. No additional data has been published by the WHO. The sponsor reports that the potential risk of bone fractures was only for the prescription PPIs and not relevant for OTC PPIs which are marketed at lower doses and shorter duration.

Proton Pump Inhibitors and Hypomagnesemia

The Agency issued a Drug Safety Communication (DSC) on March 2, 2011 which stated that prolonged use of Rx PPIs may cause hypomagnesemia. Hypomagnesemia may lead to muscle spasms, arrhythmias, and seizures. Hypomagnesemia was reported in patients treated for longer than three months but majority of the cases occurred in patients who used PPIs longer than one year. Over-the-counter PPIs marketed under brand names such as Prevacid[®] 24HR, Prilosec[®] OTC, Zegerid[®] OTC carry a low risk for developing hypomagnesemia since they are typically indicated for a 14-day course up to three times a year.

The Agency issued another DSC to physicians that they should consider obtaining serum magnesium levels prior to the initiation of Rx PPIs in patients expected to continue treatment for long periods of time as well as in patients who concomitantly take medications such as digoxin, diuretics, and heart medications. Physicians were advised to check magnesium levels periodically after initiation of PPIs in these patients.

Following this announcement, information about potential hypomagnesemia and PPIs use were added to the WARNINGS AND PRECAUTIONS sections of the Rx labels in all of the Rx PPIs: "Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically".

According to the sponsor, similar warnings and precautions were added to the label of all of the Rx PPIs in Europe. However; no warning was added to OTC PPIs, since OTC PPIs are marketed at low doses and are only intended for a 14-day course of treatment up to three times a year.

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

The Agency believes that there is a very low risk of hypomagnesemia when OTC PPIs are used according to the labeled directions.

According to the sponsor, no new data is available from the WHO regarding hypomagnesemia and PPIs.

Proton Pump Inhibitors and Clostridium difficile Associated Diarrhea

The Agency notified the public on February 8, 2012 that use of all PPIs may be associated with increased risk of CDAD and that this diagnosis should be considered by the physicians when patients present with diarrhea that does not improve.

On February 15, 2012, the Agency issued a letter to all companies that market the Rx and OTC PPIs that a labeling revision is warranted. The labeling change was an addition of “stop use and ask a doctor if you get diarrhea”. The diarrhea warning is also included in the labeling of the proposed product.

Proton Pump Inhibitors and Acute Interstitial Nephritis

Drug regulators in New Zealand, Medsafe, received numerous reports of acute renal reactions, primarily AIN, in association with the use of PPIs. On June 30, 2011, Medsafe received a total of 65 case reports of AIN associated with omeprazole (62) and pantoprazole (3). Other PPIs use is limited in New Zealand which explains the lack of association in New Zealand. The association between PPIs and AIN was first raised in 2000 by Medsafe’s Centre for Adverse Reactions Monitoring (CARM) following first seven cases of AIN associated with omeprazole use. In 2003, the Therapeutic Goods Administration (TGA), Australian Regulatory Authority, reported 18 cases of AIN and median time to onset was three months (range 12 days to 12 months). In 2003, this AE was listed in the prescribing information of all Rx PPIs approved by the Agency, EU authorities, TGA, and New Zealand.

AIN may occur at any point during PPI treatment and is generally attributed to hypersensitivity reaction to the respective PPI. In general, AIN resolves upon discontinuation of PPI treatment and majority of the cases improve with addition of corticosteroid treatment. Since the labeling changes regarding AIN were approved by the Agency in December 2014 for Prevacid[®] Rx but not for the OTC Prevacid[®] 24HR, no new safety information was added to the labeling of the proposed product.

Proton Pump Inhibitors and Clopidogrel

According to the sponsor, two authors (Gilard 2006; Gilard 2008) reported an influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin. The Agency was aware of the published articles suggesting that clopidogrel is less effective when administered with certain PPIs. Same interaction was reported by the Irish Advisory, Warnings, and Recall Notices on May 12, 2009. It was found that omeprazole is a CYP2C19 inhibitor. The inhibition

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

of this enzyme leads to reduced active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. On November 17, 2009, the Agency issued an updated Safety Information about a drug interaction between clopidogrel bisulfate and omeprazole (indicating that the anti-blood clotting effect of clopidogrel (Plavix) is reduced by almost half when these two medicines are taken by the same patient. As for other PPIs, FDA does not have enough information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to advise on their use. Based on this interaction, a drug-drug interaction warning was added to omeprazole products (prescription and OTC) in 2010 in the USA (FDA letter for CBE January, 20, 2010), Europe (Harmonization Procedure in accordance with Article 30 of Directive 2001/83/EC), Australia, Singapore and Israel. According to the sponsor, the Agency found no drug interaction between clopidogrel and lansoprazole. According to the sponsor, there is no support for causative link between lansoprazole and clopidogrel and the Agency has not required dose adjustment of clopidogrel when administered with an approved dose of prescription Prevacid[®] as stated in the Prevacid[®] (NDA 020406, Takeda) prescribing information packet.

Proton Pump Inhibitors and Methotrexate

Concomitant use of PPIs and methotrexate may increase blood level of methotrexate leading to side effects from methotrexate. The possible AEs include renal failure, anemia, gastroenteritis, arrhythmias, myalgia, diarrhea, and infections. According to the sponsor, no definite association between PPI use and increased methotrexate blood levels exist however; there are a number of studies suggestive of a possible interaction. Hence, the sponsor included “ask a doctor or pharmacist before use if you are taking methotrexate” on the label.

Proton Pump Inhibitors and Subacute Cutaneous Lupus Erythematosus

In 2013, the Netherlands Pharmacovigilance Center reported SCLE in two patients treated with omeprazole. A search in the Eudravigilance of EMA revealed 71 and the WHO database revealed 48 case reports. The odds ratio for all SCLE reports in association with PPIs was statistically significant.

Table 12: Reports of SCLE associated with PPIs in the WHO Database

Drug	WHO reports		Eudravigilance database	
	n	ROR ¹ (95% CI)	n	ROR ¹ (95% CI)
Omeprazole	24	6.8 (4.5-10.1)	22	7.6 (5.0-11.6)
Lansoprazole	10	10.0 (5.3-8.6)	30	15.0 (10.4-21.6)
Pantoprazole	7	7.3 (3.5-15.4)	12	5.2 (2.9-9.1)
Esomeprazole	7	2.5 (1.2-5.3)	5	1.9 (0.8-4.5)
Rabeprazole	0		2	
Total	48	6.0 (4.5-8.0)	71	7.2 (5.6-9.2)

WHO = World Health Organization

¹ Reporting odds ratio (ROR)

[Source: Sponsor's electronic submission, Section 5.3.5.3 page 87/114]

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

The sponsor reviewed and summarized 20 case reports of SCLE in the literature. All cases involved female patients, aged between 51 and 85. In the majority of SCLE patients, the latency ranged from three weeks to four months between start of the PPI and the onset of SCLE symptoms. Improvement was not achieved with substantial immunosuppression unless the suspected PPI was discontinued. In almost all cases, symptoms were resolved one to two months after discontinuation of the PPI. According to the sponsor, in two patients, the PPI was not discontinued and active disease was present until death which was due to another cause.

Medical Officer Comment:

Further review of 20 case reports of SCLE in the literature showed that five out of the 20 cases occurred within two weeks of PPIs initiation and the other 15 cases occurred beyond two weeks of treatment with PPIs. Four out of these five cases resolved spontaneously after withdrawal of the offending PPI and one of the five cases resolved after withdrawal of the offending PPI and treatment with hydroxychloroquine. Thirteen of the other 15 case reports of SCLE resolved spontaneously upon discontinuation of PPIs. Two out of the other 15 case reports died due to other etiologies (as reported by the authors) and their PPI treatment was not discontinued.

The Pharmacovigilance Risk Assessment Committee (PRAC) of EMA made the following recommendations regarding the safety signal in 2015:

“Based on cases from the global safety databases of Takeda, Janssen/Eisai and AstraZeneca, as well as the comments received from these MAHs (Market Authorization Holders), the PRAC has confirmed that there is sufficient evidence that indicates that SCLE is likely to be a class effect for proton pump inhibitors.

Taking into consideration the relevant data across all substances in the class, including the cases with positive re-challenge, the evidence from published literature, and the likelihood of under-reporting given that photosensitivity is a known side effect of proton pump inhibitors, the PRAC agreed that the sponsors of medicinal products containing omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole and dexlansoprazole should submit a labeling change with regard to the risk of Subacute cutaneous lupus erythematosus (SCLE).”

The PRAC recommended adding the following information to both prescription and non-prescription products:

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Table 13: PRAC Recommendations for PPI Labeling Regarding SCLE

	Special Warnings and Precautions for Use	Adverse event
Prescribing Information	Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping {Drug name}. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.	Frequency 'not known': Subacute cutaneous lupus erythematosus
Package Insert	Talk to your doctor before taking {Drug name}: <ul style="list-style-type: none">• if you have ever had a skin reaction after treatment with a medicine similar to {Drug name} that reduces stomach acid.	Possible side effects <ul style="list-style-type: none">• Frequency 'not known': rash, possibly with pain in the joints

[Source: Sponsor's electronic submission, Section 5.3.5.3 page 91/114]

Due to SCLE safety signal, the sponsor reviewed the FAERS database from 2008 to second quarter of 2015. There were 13 cases identified with lansoprazole as the primary suspect drug. Twelve of the 13 cases occurred in European female patients aged 30-80. None of the case reports were associated with Prevacid[®] 24HR OTC (NDA 022327). The sponsor has agreed to revise proposed labeling of its drug product once the Agency's decision regarding association of PPIs and SCLE is made public.

Drug Abuse Warning Network (DAWN)

According to the sponsor, the DAWN database is currently being combined with the National Hospital Ambulatory Medical Care Survey data and the National Hospital Discharge Survey data in a new endeavor called the National Hospital Care Survey, managed by the National Center for Health Statistics. The transition is expected to take until 2016 and no updates to the DAWN database are expected beyond 2011 data. The sponsor evaluated the DAWN database from 2004 to 2011. Frequency of reports, case type, basic demographic information, and outcome were assessed. Lansoprazole is not individually mentioned, but its class of drugs, PPIs, is listed in the DAWN national estimate of drug-related emergency department visits. Currently, there are six PPIs that are FDA-approved and marketed. Individual data of PPIs are unavailable hence the data presented does not represent lansoprazole alone. The sponsor states that the actual emergency department visits attributed to the abuse and misuse of lansoprazole is likely less than what is represented below.

Table 14 shows weighted estimates of emergency department visits by gender related to PPIs.

Table 14: Weighted Annual Estimates of Emergency Department Visits by Gender

Gender	2004	2005	2006	2007	2008	2009	2010	2011
Male	*	595	1,618	2,167	3,727	2,692	3,933	3,363

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Female	1,966	1,553	2,135	3,037	2,552	3,294	4,946	2,310
Total	3,487**	2,149**	3,754**	5,205**	6,279	5,986	8,879	5,673

*Indicates that the figure does not meet DAWN standards of precision. An estimate with a relative standard error greater than 50%, an unweighted count, or estimate less than 30 is suppressed.
 **The totals for the years 2004-2007 do not equal the sum of the male + female total, this discrepancy was present in the DAWN database and was preserved to maintain the integrity of the data
 Source: DAWN database

[Source: Sponsor’s electronic submission, Section 5.3.5.3 page 93/114]

Table 15 shows the weighted annual estimates of emergency department visits by age groups. According to the sponsor, all of the age groups below 35 did not meet the DAWN parameters of precision, suggesting that the majority of abuse or misuse cases occurred with users 35 and older.

Table 15: Weighted annual estimates of emergency department visits by age group

Age range	2004	2005	2006	2007	2008	2009	2010	2011
0-5	*	*	*	*	*	*	*	*
6-11	*	*	*	*	*	*	*	*
12-17	*	*	*	*	*	*	*	*
18-20	*	*	*	*	*	*	*	*
21-24	*	*	*	*	*	*	*	*
25-29	*	*	*	*	*	*	*	*
30-34	*	*	*	*	*	*	*	*
35-44	*	484	702	875	1,227	717	*	*
45-54	174	406	930	992	905	1,531	4,148	*
55-64	*	*	*	*	2,575	1,233	1,844	1,602
65 +	*	*	*	1,342	699	1,441	1,101	1,269

*Indicates that the figure does not meet DAWN standards of precision. An estimate with a relative standard error greater than 50%, an unweighted count, or estimate less than 30 is suppressed.
 Source: DAWN database

[Source: Sponsor’s electronic submission, Section 5.3.5.3 page 94/114]

The DAWN ethnicity database suggests that majority of the abuse and misuse cases occurred in white patients.

The sponsor reports that overall majority of patients were sent to an inpatient unit and not the intensive care unit, detox unit, or psychiatric unit. The estimated deaths associated with PPIs related to emergency department visits was either too small, or had a relative standard error greater than 50%. According to the sponsor, the combination of low number of case reports and the number of patients admitted to the intensive care unit suggests that most events were

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

less serious in nature which as observed with NPDS data outlined previously in this review. The NPDS data suggested that most poisoning events and misuse/abuse events were considered to have little to no toxic effect.

Literature Review

The sponsor conducted a PubMed query for information in the published literature supporting the safety of lansoprazole on May 21, 2015. The search included the search word "lansoprazole" and had limits of "English", "humans", and "clinical trials", and had a limited date range from 2008 to 2014. Relevant publications that presented new safety data and exposure to lansoprazole were identified and reviewed. A total of 30 studies were identified from this PubMed search strategy. For the 120-day Safety Update, the PubMed database was searched through September 15, 2015 for relevant publications. A total of four publications that presented clinical safety data for lansoprazole were identified and reviewed by the sponsor (one retrospective study and three clinical studies).

According to the sponsor, most of the studies used a higher dose of lansoprazole which was administered for a longer duration than 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. Serious AEs were also reported, but were typically identified as not being treatment-related.

According to the sponsor, during the time period covered for the 120-day Safety Update, a retrospective study of GERD patients exposed to PPIs from 1994 to 2012 was published that reported associations (based on pharmacovigilance algorithms) between PPI use (including lansoprazole, omeprazole, and pantoprazole) and cardiovascular complications such as myocardial infarctions. Additionally, a survival analysis in prospective cohort of the patients showed a two-fold increase in the association of PPIs use and cardiovascular mortality. The study did not account for drug dosage or duration of use. The sponsor states that these findings differ from a retrospective study by Rossini et al. (Rossini, 2011) which found no association between PPI use and in-hospital major adverse cardiac events (MACEs), 1-year MACEs, death, or stent thrombosis in patients who underwent drug-eluting stent implantation. The sponsor reports that as part of the 120-day Safety Update, cardiovascular safety signals have not been associated with PPI usage in pharmacovigilance databases as noted in Sections 2.7.4.6.2 and 2.7.8.4.2 in the submission of this NDA. Therefore, further research will be needed to verify the association between PPI use and cardiovascular risk and determine whether the observations are causative and not just associative.

The sponsor's summary of published literature was reviewed. Published literature reporting serious AEs was closely examined. Brief summary is noted below:

- The sponsor reports that articles by Zhang et al., in 2012 noted five of 12

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

subjects reported a total of six AEs, all of them were mild in nature and resolved by study completion. The AEs included urine occult blood, urinary leukocyte positive test, anemia, and leucopenia. The subjects received single intravenous (IV) lansoprazole with dose range of 15 mg to 60 mg.

- The same authors published another report in 2013 which involved four of 12 subjects reporting a total of four AEs, all of which were mild in severity and resolved by one week of study completion. The AEs included two subjects with urine occult blood, one subject with elevated ALT, and one subject with leucopenia. The subjects received 30 mg IV on Day 1; 30 mg IV twice a day on Day 2 to 5, and 30 mg IV on Day 6. There were no significant clinical findings in vital signs, biochemistry, or ECG.
- One case report of toxic epidermal necrolysis (15 days after initiation of lansoprazole) was treated with discontinuation of lansoprazole, skin debridement, and human IV immunoglobulins.
- One case report of lansoprazole-induced interstitial nephritis in a renal transplant patient was treated successfully with discontinuation of lansoprazole, famotidine, and pulse doses of methylprednisolone.
- Concomitant use of lansoprazole and warfarin in CYP2C19 intermediate metabolizer patients increases the risk of bleeding due to exaggerated response to warfarin.
- One case report of idiosyncratic reaction to lansoprazole 10 days after initiation causing cholestatic liver injury and hypersensitivity pneumonitis treated with discontinuation of lansoprazole and high doses of corticosteroids.
- Numerous studies reporting increase serious AEs in neonates and children treated with lansoprazole. Children with poor metabolizer phenotype developed uncontrolled asthma six months after initiating lansoprazole secondary to altered response to respiratory infections.

Medical officer comment:

Information provided in the literature search including the 120-day Safety Update does not significantly alter the known safety profile of lansoprazole especially if it will be used appropriately in the OTC setting.

8.8.2. Expectations on Safety in the Postmarket Setting

The proposed product is expected to maintain the same safety profile as the LD. The new risks associated with the proposed product are related to the orally disintegrating technology. All of the excipients in the proposed formulation are below the maximum potency of the Inactive Ingredient Database (IID) for oral solid dosage form and most of them are present in orally disintegrating tablets listed in the IID. The sponsor performed safety analyses on four excipients not listed for ODT products in the IID, and have found that the four excipients in its

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

product are safe and qualified for intended use.

8.9. Additional Safety Issues From Other Disciplines

Reviews from other disciplines are pending at the time of this review.

8.10. Integrated Assessment of Safety

The sponsor supports the safety of its NDA 208025 by information obtained from the PK studies and postmarketing information for lansoprazole as well as updated literature review.

The sponsor's original submission includes postmarketing data from:

- National Poison Database System (NPDS) from 2008 to 2014
- FDA Adverse Events Reporting System (FAERS) from 2008 to second quarter of 2014
- World Health Organization (WHO) from 2008 to April 2015
- Drug Abuse Warning Network (DAWN) from 2004 to 2011 (Currently undergoing transition to the National Hospital Care Survey, data beyond 2011 unavailable)
- Literature Search from 2008 to 2014

The sponsor also relies on the Agency's findings of safety and efficacy for listed drug, Prevacid[®] 24HR (NDA 022327, Novartis).

The sponsor conducted 120-day Safety Update through September 15, 2015 which included data from the NPDS, FAERS, WHO, DAWN, and literature search.

The postmarketing data and literature search was discussed in detail in the sections above.

Lansoprazole (Prevacid[®], NDA 020406, Takeda) by prescription was first approved in May 1995. Subsequently, Prevacid[®] 24HR (NDA 022327, Novartis) was approved for OTC use in May 2009 by the Agency for the treatment of heartburn. Consumers have been safely self-treating frequent heartburn with OTC Prevacid[®] 24HR for the last seven years and PPIs in general since 2003 with Prilosec[®] OTC. The safety profile of lansoprazole has been well established for both Rx and OTC use.

The PPIs are usually well tolerated and the AEs are generally mild in nature and reversible. The most common AEs associated with lansoprazole ODT include headache and nausea. The most common AEs associated with Prevacid[®] 24HR include diarrhea, headache, abdominal pain, nausea, and constipation. The AEs profile of lansoprazole is consistent with the worldwide experience with lansoprazole according to the sponsor. The label for Prevacid Rx has the

Clinical Review

Ketan P. Parikh, M.D.

NDA 208025 / SN 0004

Lansoprazole Delayed-Release Orally-Disintegrating Tablets

following warnings:

- Symptomatic response with Prevacid does not preclude the presence of gastric malignancy
- Acute interstitial nephritis has been observed in the patients taking PPIs including lansoprazole
- Daily long-term use (e.g., longer than three years) may lead to malabsorption or a deficiency of cyanocobalamin (vitamin B₁₂ deficiency)
- Proton-pump inhibitor therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea
- Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs

Many of the above safety concerns are associated with long term use of PPIs. As the indication for lansoprazole ODT OTC is for a 14-day course in the treatment of frequent heartburn, these safety concerns are of less importance for OTC consumers. Prevacid[®] 24HR OTC capsules were approved for marketing in May 2009; the DFL, under “Stop use and ask a doctor if” includes “you get diarrhea” to address the safety concern related to *Clostridium difficile* associated diarrhea.

In October 2014, the Agency issued a class labeling change request for PPIs to add drug-drug interaction warning with mycophenolate mofetil to the DFL Warnings section of the approved Prevacid[®] 24HR labeling in NDA 022327. This Warning was included in the labeling of the proposed product.

The sponsor states that NDA 020406 (Prevacid[®] Rx, Takeda) labeling states that over 10,000 patients have been treated with Prevacid[®] in Phase 2 or Phase 3 clinical trials involving various doses and duration of treatment. Prevacid[®] Rx was first approved for marketing in 1995 and Prevacid[®] 24HR OTC was approved in 2009. In the USA, more than (b) (4) Prevacid[®] Rx and (b) (4) Prevacid[®] 24HR OTC doses were distributed in 2014-2015 according to the distribution data provided to the Agency by Takeda and Novartis, respectively.

Safety Conclusions

Both the LD and the TD, under fed and fasted conditions, were well tolerated with no unexpected safety findings. No deaths occurred during the PK studies. Most participants in the PK studies (245 out of 289, approximately 85%) did not report any AEs during the study; 11% reported one AE and 4.1% reported two AEs. There were a total of 62 TEAEs reported in the PK studies. Most were mild in nature and none were considered serious according to the sponsor. Only 35 of these AEs were related to lansoprazole. Headache was the most frequently reported TEAE, which was reported in 17 subjects.

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

According to the sponsor, events were similar across all treatment groups, and specifically there were no differences in the events observed for the proposed ODT tablets and the LD.

There were no deaths or serious AEs in the PK studies.

A total of twelve subjects withdrew from some of the treatment phases in the PK studies and none were due to serious AEs. Majority of them were due to personal reasons, narratives provided limited information on these patients.

In the Project 120383, subject 47, a 35-year-old female experienced a significant AE, “abortion” approximately 25 days following lansoprazole administration in Period 2 (Treatment D, Prevacid[®] 24HR). The urine pregnancy test was performed prior to Period 1 and 2 on this subject and both were negative, however; the serum pregnancy test prior to dose administration in Period 3 was positive. The subject confirmed that she always used a contraceptive device as instructed. The principal investigator had a discussion with the subject regarding uncertainty of human fetus risk associated with the use of lansoprazole. The subject was administered only 2 doses of the study medication after the start of her last menstrual period. The subject terminated her pregnancy and the event was labeled as AE “abortion”. This AE was judged to be unrelated to the study medication by the sponsor.

In the Project 120384, subject 7, a 39-year-old female experienced significant TEAEs, “headache” and “hot flush” approximately 5 hours and 1 hour respectively, prior to drug administration in Period 2. Subject was withdrawn from the study as a precautionary measure. The subject was placed in recumbent position and vital signs were carefully monitored until resolution of her symptoms.

Some subjects withdrew due to poor vein access and dizziness after blood draw.

After reviewing the information submitted in this NDA, 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.

9 Advisory Committee Meeting and Other External Consultations

None recommended.

10 Labeling Recommendations

10.1. Prescribing Information

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Not applicable as this is an OTC product.

10.2. Patient Labeling

Not applicable as this is an OTC product.

10.3. Nonprescription Labeling

A formal labeling review will be performed by the IDS team in DNDP, see the review by Mary Vienna, RN, MHA. The sponsor did not provide a proprietary name for review by DMEPA. The sponsor's proposed DFL and principal display panel for lansoprazole ODT tablets are shown in Figures 1 and 2, respectively.

Medical Officer Comment:

The Drug Facts Label is similar to that of the listed drug, Prevacid[®] 24HR OTC capsules, except for "do not take this medicine with alcohol" under "Directions", inactive ingredients and revised content under "other information". The sponsor does not seek any additional claims than what is allowed for the other approved OTC PPIs, including Prevacid[®] 24HR OTC capsules. Language addressing the concerns regarding drug-drug interactions, as well as signs and symptoms of serious conditions are appropriately labeled. Class labeling change addressing the risk of Clostridium difficile associated diarrhea is on the Drug Facts Label ("Stop use and ask a doctor if ...you get diarrhea"). In addition, the class labeling changes requiring methotrexate and mycophenolate mofetil to be included under the section "Ask a doctor or pharmacist before use if you are taking:" are included.

Currently, "do not chew or crush tablets" is the fourth bullet in the subsection "14-Day Course of Treatment" under the "Directions" section. The sponsor states that any damage to the (b) (4) coated pellets would alter the drug release profile, by reducing the resistance of the (b) (4) pellets which contain the active ingredient, lansoprazole, to dissolution in the gastric fluids, and therefore change the pharmacokinetics similarity to the LD.

It is this reviewer's opinion that the following labeling changes be considered for the proposed product's DFL:

- *Phrase pertaining to subsection "14-Day Course of Treatment" under "Directions" section, "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.*

Clinical Review
Ketan P. Parikh, M.D.
NDA 208025 / SN 0004
Lansoprazole Delayed-Release Orally-Disintegrating Tablets

Figure 1: Sponsor's proposed Drug Facts Label for lansoprazole 15 mg ODT tablets



[Source: Sponsor's electronic submission, Section 1.14.1.1 inner carton page 1/1]

Figure 2: Lansoprazole 15 mg ODT Principle Disolv Panel

(b) (4)



[Source: Sponsor's electronic submission, Section 1.14.1.1 inner carton page 1/1]

11 Risk Evaluation and Mitigation Strategies (REMS)

There are no special post-market risk evaluation and mitigation strategies recommended beyond routine pharmacovigilance.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable.

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3. Recommendations on REMS

Not applicable.

12 Postmarketing Requirements and Commitments

None recommended beyond routine pharmacovigilance.

13 Appendices

13.1 References

- ACP Medicine Online Chapter VIII. (n.d.). Ectopic Pregnancy and Spontaneous Abortion. Retrieved from Ectopic Pregnancy and Spontaneous Abortion.
- Blum, R. (1996). Lansoprazole and omeprazole in the treatment of acid peptic disorders. *Am J Health-Syst Pharm*, 53:1401-15.
- CDC. (n.d.). *Birth Defects*. Retrieved 03 11, 2016, from CDC: <http://www.cdc.gov/ncbddd/birthdefects/facts.html>
- Diav-Citrin, O. (2005). The safety of PPIs in pregnancy: A multicentre prospective controlled study. *Alimentary Pharmacology and Therapeutics*, 269-275.
- El-Serag, H. B. (2014). Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*, 871-880.
- Gremse, D. (2002). Pharmacokinetics and pharmacodynamics of lansoprazole in children with gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr*, 35 Suppl 4:S319-S326.
- Kahrilas, P. (2015). Diseases of the Esophagus. In D. Kasper, *Harrison's Principles of Internal Medicine, 19e* (p. 1130). New York, NY: McGraw-Hill.
- Klotz, U. (2009). Proton pump inhibitors--their pharmacological impact on the clinical management of acid-related disorders. *Arzneimittelforschung*, 59(6):271-82.
- Kushner, P. (2009). Lansoprazole 15 mg once daily for 14 days is effective for treatment of frequent heartburn: results of 2 randomized, placebo-controlled, double-blind studies. *Postgraduate Medicine*, 67-75.
- McQuaid, K. (2015). Gastrointestinal Disorders. In M. Papadakis, *Current Medical Diagnosis & Treatment 2015* (p. Chapter 15). New York, NY: McGraw-Hill.
- Nikfar, S. (2002). Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. *Dig Dis Sci*, 1526-9.
- Peura, D. (2009). Clinical trial: lansoprazole 15 or 30 mg once daily vs. placebo for treatment of frequent nighttime heartburn in self-treating subjects. *Aliment Pharmacol Ther*, 459-468.
- Rossini, R. (2011). Safety of clopidogrel and proton pump inhibitors in patients undergoing drug-eluting stent implantation. *Therapy and Prevention*, 199-205.

Clinical Review
 Ketan P. Parikh, M.D.
 NDA 208025 / SN 0004
 Lansoprazole Delayed-Release Orally-Disintegrating Tablets

13.2 Financial Disclosure

Covered Clinical Study (Name and/or Number):

Randomized, open-label, 4-way crossover design, bioequivalence study of lansoprazole delayed-release orally disintegrating tablet 15 mg (DPT) and Prevacid[®] 24HR (LD) following a 15 mg dose in healthy subjects under fasting conditions (Project 120383).

Randomized, open-label, 2-way crossover design, comparative bioavailability, food-effect study of lansoprazole delayed-release orally disintegrating tablet 15 mg (Project 120384).

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>19</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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

/s/

KETAN P PARIKH
05/04/2016

FRANCIS E BECKER
05/04/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 208025
Resubmission / SN 0004

Applicant: Dexcel Pharma
Technologies LTD

Stamp Date: August 13, 2015

Drug Name: OTC Lansoprazole
ODT

NDA/BLA Type: 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic submission only. One volume, SN0004
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			See DNNDP labeling team's filing review.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			No formal ISE but Summary of Clinical Efficacy located in 2.7.3
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	505 (b)(2) Prevacid 24HR 15 mg delayed release capsules (Reference Drug (RD)) by Takeda Pharmaceuticals America, Inc., is the reference drug with 505(b)(1) NDA 022327 approved on 05/18/2009.			
505(b)(2) Applications					
13.	If appropriate, what is the relied upon listed drug(s)?	X			See 12
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	X			Project 120383: Single-dose (15 mg) fasted BE study in 72 healthy subjects
15.	Describe the scientific bridge (e.g., BA/BE studies)	X			Project 120384: Single-dose (15 mg)

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	efficacious?				NDA.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	DNDP did not require consumer behavior studies for this NDA.
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Full waiver granted.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No clinical efficacy studies were conducted for this NDA.
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	See Clinical Pharmacology Filing Review.
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and	X			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts)?				
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			It was included in SN0000 but not with SN0004.
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ketan P. Parikh, MD

 Reviewing Medical Officer

October 9, 2015

 Date

Francis E. Becker, MD

 Clinical Team Leader

October 9, 2015

 Date

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

/s/

KETAN P PARIKH
10/09/2015