

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208056Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review-Addendum

This addendum updates the CDTL review, dated January 11, 2016, to include the following information on waivers for pediatric studies, which will be communicated to the applicant in the Approval Letter. Refer to the Approval Letter for final language, agreed pediatric requirements, and timelines for submission.

- We are waiving the pediatric study requirement for pediatric patients from birth to less than 1 month of age for the indication of maintaining healing of all grades of erosive esophagitis (EE) because the necessary studies are impossible or highly impracticable. This is because the incidence of EE in infants from birth to less than one month of age is low.
- We are waiving the pediatric study requirement for pediatric patients less than 12 months of age for the indication of treatment of heartburn associated with symptomatic non-erosive GERD. There is evidence strongly suggesting that the drug would be ineffective in this pediatric age group and that conservative treatment of signs and symptoms associated with non-erosive GERD is the recommended approach.

In addition, the following revisions were made to Section 9: Pediatrics:

- No changes have been made to the pediatric program since the Agreed iPSP, dated (b) (4) December 11, 2014. The pediatric plan was presented to PeRC on December 9, (b) (4) 2015.

Date	January 11, 2016
From	Juli Tomaino MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 208056
Supplement#	
Applicant	Takeda Pharmaceuticals, USA, Inc.
Date of Submission	March 26, 2015
PDUFA Goal Date	January 26, 2016
Proprietary Name / Established (USAN) names	Dexilant SoluTab [®] (dexlansoprazole delayed-release orally disintegrating tablet)
Dosage forms / Strength	30 mg oral
Proposed Indication(s)	(b) (4) 2. Maintaining healing of EE and relief of heartburn, 3. Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease GERD
Recommended:	Approval of Dexilant SoluTab [®] 30 mg for the following indications: - Maintaining healing of erosive esophagitis and relief of heartburn. - Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease. (b) (4)

1. Introduction

On March 26, 2015, Takeda Pharmaceuticals, USA, Inc. (the applicant) submitted a new drug application (NDA) to support marketing approval of a new formulation of dexlansoprazole, Dexilant SoluTab[®] (dexlansoprazole delayed-release orally disintegrating tablets [ODT]). Dexlansoprazole is currently available in two dose strengths, 30 mg and 60 mg, as Dexilant delayed-release capsules, approved January 30, 2009 (NDA 22287). (b) (4)

Dexilant delayed-release capsules, based primarily on the results of two bioequivalence studies. The currently labeled indications and dosage for Dexilant delayed-release capsules include the following:

- Healing of all grades of erosive esophagitis (EE): 60 mg once daily for up to 8 weeks.
- Maintaining healing of EE and relief of heartburn: 30 mg once daily for up to 6 months.
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD): 30 mg once daily for 4 weeks.

In support of this NDA, the applicant conducted seven phase 1 studies (6 bioavailability/bioequivalence [BA/BE] studies and 1 in-vivo disintegration time study) in healthy subjects to support the indications listed above. No additional clinical efficacy or safety trials evaluating the dexlansoprazole ODT formulation were conducted.

The review of this application was conducted as a Standard review with a Prescription Drug User Fee Act (PDUFA) goal date of January 26, 2016. All of the review disciplines recommend in favor of approval for the indications of maintaining of healing of EE and relief of heartburn, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) (b) (4)

the data provided failed to establish bioequivalence between two dexlansoprazole ODT 30 mg tablets and one Dexilant 60 mg capsule. This issue will be explained in greater detail through this review.

This memo summarizes the information contained in NDA 208056 and discusses the recommendations made by each review discipline.

1) Background

Clinical Background

Gastroesophageal reflux disease (GERD) is characterized by the presence of abnormal reflux of acid into the esophagus from the stomach, with an estimated prevalence of approximately 10-20% in the Western population. There is a lower prevalence in Asia and trend toward higher prevalence in North America as compared to Europe. Of note, the estimate is based on the classic symptoms of GERD, which are heartburn and regurgitation.¹ Atypical symptoms include dyspepsia, epigastric pain, nausea, bloating, and belching but these symptoms often overlap with other etiologies. Symptomatic non-erosive GERD and erosive esophagitis (EE) both result from GERD. Erosive esophagitis (EE) is characterized by erosions and ulcerations in the esophagus, diagnosed via endoscopy, whereas symptomatic non-erosive GERD may have little to no endoscopic findings. Complications of untreated or poorly controlled GERD include EE, esophageal strictures, Barrett's esophagus, and adenocarcinoma.² Management of GERD involves acid suppression therapy (e.g., H₂-receptor antagonists or proton pump inhibitors) and lifestyle modification. For severe, refractory cases, surgical intervention may be an option.

Dexlansoprazole is a proton pump inhibitor (PPI) that inhibits the H⁺/K⁺/ATPase system in the gastric parietal cells. Dexlansoprazole is the R-enantiomer of the racemate, lansoprazole, which was approved for use in adults in May 1995. Dexlansoprazole (Dexilant delayed release capsules) was approved on January 30, 2009 for use in adults for healing of all grades of erosive esophagitis (EE), maintaining of healing of EE, and treating heartburn associated with symptomatic non-erosive GERD. The indication for maintaining of healing of EE was

¹ Dent, J., et al. Epidemiology of Gastro-oesophageal Reflux Disease: A Systematic Review. Gut 2005; 54:710-717.

² Katz, P., Gerson, L., Vela, M.. Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol 2013; 108:308–328.

expanded to include the relief of heartburn in 2011. An overview of the regulatory history is described below.

Regulatory Background

January 30, 2009: Dexilant (dexlansoprazole) delayed-release capsules, 30 mg and 60 mg, were approved for adults for the indications of healing of all grades of erosive esophagitis (EE), maintaining of healing of EE, and treating heartburn associated with symptomatic non-erosive GERD (sGERD). The dosage for the healing of EE is 60 mg once daily for up to 8 weeks, while the dosage for the maintenance of healed EE and relief of heartburn, and treating heartburn associated with sGERD is 30 mg once daily for up to 6 months and 4 months, respectively.

March 3, 2010: A pre-IND (PIND) meeting was held to discuss the proposed development plans for dexlansoprazole orally disintegrating tablet (ODT) formulation. Refer to meeting minutes, dated April 1, 2010, under IND 106858 for complete details. Key discussion items included recommendations that the sponsor consider reformulation of the ODT product to ensure bioequivalence with the Dexilant capsules in both the fasted and fed states since bioequivalence was not established in the fasted state. Additionally, the Division stated that a PK comparability study in the fasted state is more sensitive than in the fed state. (b) (4)

The sponsor was referred to the guidance for industry on bioequivalence.

June 27, 2011: IND 106858 was submitted to evaluate the 30 mg orally disintegrating tablet in a phase 1 PK study. IND 106858 was found to be safe to proceed.

June 17, 2011: An efficacy supplement for Dexilant delayed-release capsules (NDA 22287) was approved that expanded the indication for maintaining healing of EE to also include the relief of heartburn.

November 2, 2011: Takeda requested a meeting to discuss the development plans for the ODT formulation. The meeting was cancelled by the sponsor upon receipt of the preliminary meeting responses, dated February 3, 2012. Key discussion items included comments from the Division noting differences in the mean concentration-time profile of the ODT as compared to the Dexilant capsules. In addition to bioavailability studies with the 30 mg ODT, the sponsor was advised to also evaluate the relative bioavailability between two 30 mg dexlansoprazole ODT and one Dexilant 60 mg capsule to inform the safety evaluation. Also, detailed advice from CMC was provided. Refer to meeting minutes, dated February 3, 2012, for the full details.

September 3, 2014: A CMC Type B pre-NDA meeting was held. Advice on the acceptability of the proposed specification for both release and stability, dissolution methods, disintegration

time, and manufacturing processes were provided. Refer to the meeting minutes, dated September 29, 2015, for details.

December 11, 2014: The sponsor was notified of agreement to the iPSP (Pediatric study plan), submitted November 19, 2014.

February 13, 2015: Type C meeting responses in the form of written responses were provided to the sponsor to provide further feedback on the content, organization, and format of the planned dexlansoprazole ODT NDA in eCTD format. Refer to the meeting minutes dated, February 13, 2015, for details.

March 26, 2014: NDA 208056 was submitted to support product labeling for dexlansoprazole ODT. The NDA included seven phase 1, open-label bioavailability/bioequivalence (BA/BE) studies conducted in healthy adults.

Submission and Review

The NDA was received electronically on March 26, 2015, and granted a Standard Review status with a goal date of January 26, 2016. The review disciplines have written review documents. The primary review documents relied upon in my CDTL memo are listed below:

Review Team - Disciplines	Name(s) of discipline reviewers
Medical Officer Review/CDTL	J. Tomaino, MD
Nonclinical (DGIEP)	K. Zhang, PhD, D. Joseph, PhD, dated 12/22/15
OPQ Review Drug Substance (OPQ/ONDP/DNDAPI/ Branch II)	B. Stevens, PhD, MPH, D. Christner, PhD, dated 12/21/15
OPQ Review Drug Product and Environmental Assessment (ONDP/DNDP II/ Branch IV)	H. Shafiei, PhD, M. Rhee, PhD, dated 12/24/15
Application Technical Lead (ONDP/DNDP II/ Branch IV)	H. Shafiei, PhD 12/24/15
OPQ Microbiology and Process Review (OPF/Division of Process Assessment II/Branch V)	Y. Tang, PhD; C. Cruz, PhD, dated 12/21/15
OPQ Review Facility (OPF/DIA/Branch III)	M. Heayn, J. Williams, Grace E McNally, X. Shen, dated 12/23/2015
OPQ Biopharmaceutics (OPQ/DB/Branch II)	P. Duan, PhD, T. Chen, PhD, dated 11/19/15
Clinical Pharmacology Review (OCP/DCP3)	D. Jappar, PhD, S. Lee, PhD., H. Ahn, PhD, dated 12/23/15
Labeling review (OPDP, DMPP)	M. Patel, PharmD, K. Dowdy, RN, BSN, dated 12/2/15, and 12/22/15
OSI (Bioequivalence Establishment Inspection)	M. Heayn/S. Nkah (NAI decline to inspect due to previous inspection history)
Labeling review (OSE/DMEPA)	S. Abraham, RPh, K. Worthy, PharmD, L. Merchant, PharmD, dated 10/15/2015
Other: Consultation review (DPMH)	Maternal health review: M. Dinatale, MD, T. Johnson, MD, dated 11/30/15. Pediatric review: A. Taylor, MD/H. Sachs, MD, dated 12/20/15

DGIEP: Division of Gastroenterology and Inborn Errors Products, OPQ: Office of Pharmaceutical Quality, ONDP: Office of New Drug Products, DNDP: Division of New Drug Products, DNDAPI: Division of New Drug Active Pharmaceutical Ingredient, OPF: Office of Process and Facilities, OCP: Office of Clinical Pharmacology, DCP3: Division of Clinical Pharmacology 3, OPDP: Office of Prescription Drug Promotion, DMPP: Division of Medical Policy Programs, DMEPA: Division of Medical Error Prevention and Analysis, DPMH: Division of Pediatric and Maternal Health

The reader is referred to the primary review documents for more specific details of the application and review conclusions. This memo summarizes selected information from the primary review documents.

2) CMC

The quality reviewers have recommended approval of NDA 208056 with a drug product expiration dating period of 30 months, and I agree with their assessments. The quality reviewers concluded that there are sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance and drug product. I have summarized the key review findings below. The reader is referred to the OPQ Integrated Quality Assessment review, dated 12/24/2015, for the complete information.

CMC/Drug Substance Quality Review

The quality reviewers concluded that dexlansoprazole is produced by a robust manufacturing process with the appropriate control strategy that enables production of the active pharmaceutical ingredient (API) with consistent quality. As described in the CMC review, this API is tested and released according to a specification that assures the identity, strength, purity, and quality of the API at release and throughout the designated retest period. The reviewers state that the stability data provided in the referenced product, Dexilant delayed-release capsule (NDA 22287), support the proposed retest date of (b) (4) for the drug substance.

CMC/Drug Product Quality Review

As described in the drug product quality review, dexlansoprazole ODT consists of two types of dexlansoprazole enteric coated microgranules (b) (4)

Dexlansoprazole ODT will be packaged (b) (4)

in a 100-unit per package configuration. The drug product specification includes testing and acceptance criteria for appearance, identity, assay, related substances, content uniformity, (b) (4) disintegration, dissolution, and bioburden. Based on the biopharm, microbiology, and drug product reviewers' assessments, the proposed specification for dexlansoprazole ODT is adequate to assure the identity, strength, purity, and quality of the drug product at release and throughout the proposed product shelf-life.

Facilities review/inspection

The Office of Process and Facility has issued an "approval" recommendation for all facilities involved in this NDA. The reviews by Drs. J. Williams, G. McNally, and X. Shen concluded that there appear to be no risks to the manufacturing process or final product based on the results of the facilities inspection and the inspectional history.

CMC/Manufacturing Process Review

The quality reviewers concluded that the applicant has provided sufficient information to show that the manufacturing process is adequate to produce a consistent drug product that meets the proposed drug product specification. Therefore, from the manufacturing process perspective, the reviewers have recommended approval.

CMC/Biopharmaceutics Review

The biopharmaceutics reviewers recommend approval of this application. The reviewers concluded that the dissolution acceptance criteria in the proposed specification and the justification for the orally disintegrating tablet (ODT) designation were appropriate. Of note, an alcohol dose dumping effect was identified; however, this finding will be discussed in the clinical pharmacology section of this document.

CMC/Microbiology Review

The applicant's initial proposal not to conduct microbial limit test (MLT) was not acceptable per 21 CFR 211.188. After two rounds of Information Requests, the applicant agreed to conduct MLT for product release and for stability (see amendment, dated 09/15/2015). The quality reviewers determined that the MLT test methods and specification limits are in compliance with USP <61>, <62> and <1111>. Therefore, Dr. Y. Tang and Dr. C. Cruz concluded that the information provided is adequate for approval of this application.

CMC/Environmental Assessment

The quality reviewers granted the applicant's request for the categorical exclusion from the environmental assessment.

The CMC/quality reviewers have not recommended PMCs or PMRs. The final labeling includes the recommended changes by the quality reviewers.

3) Nonclinical Pharmacology/Toxicology

The nonclinical team has recommended approval, and I agree with the recommendation. For complete information, the reader is referred to the Pharmacology/Toxicology review by Dr. K. Zhang (primary review) and Dr. D. Joseph (secondary review), dated 12/22/2015. I have summarized the key review findings below.

As described above in the CMC/Drug Product Quality Review summary, dexlansoprazole ODT is comprised of two types of microgranules, (b) (4). The composition of the microgranules is described in the nonclinical review, dated 12/22/15. The nonclinical reviewers commented on the novel excipients and in the nonclinical review, Dr. Zhang and Dr. Joseph explain that for most of the excipients, the daily intake at the proposed maximum dose does not exceed the daily intake of other approved oral formulations, based on the FDA inactive ingredient databases. However, the excipient "strawberry durarome" is not found in the FDA databases. The nonclinical reviewers reviewed Drug Master File (DMF) (b) (4) and noted that a letter of authorization for DMF (b) (4) was provided in this application. Based on the information provided in the DMF for the individual ingredients

in strawberry durarome, and given the proposed maximum dose for dexlansoprazole ODT, the nonclinical reviewers concluded that there are no safety concerns about the use of this favoring in dexlansoprazole ODT.

Another excipient, (b) (4) methacrylate copolymer, (b) (4) has been used at lower amounts in two other approved drug products. Since the proposed maximum daily dose of (b) (4) in dexlansoprazole ODT is higher than in the other approved products, nonclinical data were needed to assess the safety of this excipient. The supporting nonclinical data for (b) (4) is contained in DMF (b) (4) and a letter of authorization was provided in this application. The nonclinical reviewers concluded that the maximum daily dose of (b) (4) is less than the NOAEL (1500 mg/kg/day) identified in the 26-week oral toxicity study in rats; therefore, the NOAEL provides a safety margin of (b) (4)-fold based on a mg/kg comparison to the maximum dose in adults, assuming minimal systemic absorption. The nonclinical reviewers concluded that the (b) (4) contained in dexlansoprazole ODT does not raise safety concerns for use in adults, and the overall toxicity data can also support higher mg/kg doses of (b) (4) that would occur with administration of dexlansoprazole ODT in the pediatric population.

The drug product long-term stability samples contain, (b) (4) a degradation impurity. (b) (4) is a (b) (4). The maximum potential daily intake of (b) (4) is (b) (4) mcg/day, which exceeds the ICH qualification threshold of (b) (4) mcg/day. To support qualification of (b) (4), a 4-week oral toxicity study in rats using a fixed dose of dexlansoprazole with and without (b) (4) was submitted in this NDA. The study was reviewed by Dr. K. Zhang and Dr. D. Joseph, who concluded that the dose of (b) (4) mg/kg/day of impurity (b) (4) (human equivalent dose = (b) (4) mg/kg/day) was well tolerated. Since this dose is approximately (b) (4) times the maximum potential daily dose at the proposed limit of (b) (4)%, the nonclinical reviewers determined that impurity (b) (4) is considered to be qualified at (b) (4)%.

The reviewers have not recommended PMCs or PMRs. The final labeling includes recommended changes by the nonclinical reviewer and the DPMH consultants.

4) Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology team concluded that the NDA is partially acceptable for approval, provided an agreement on labeling is reached. I agree with the recommendation. The clinical pharmacology reviewers recommend approval of dexlansoprazole ODT for the following two indications based on the established bioequivalence between dexlansoprazole ODT 30 mg and Dexilant capsule 30 mg.

- Maintaining healing of erosive esophagitis and relief of heartburn.
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

(b) (4)

the data provided in this submission failed to establish bioequivalence between two dexlansoprazole ODT 30 mg tablets and one Dexilant delayed-release 60 mg capsule.

(b) (4)

The reader is referred to the clinical pharmacology review by Dr. D. Jappara (primary review), and Drs. S. Lee and H. Ahn (secondary reviewers), dated 12/23/2015, for complete information. I have summarized the key review findings below.

Bioequivalence 30 mg strength

Study TAK-390MR(OD)-105 was an open-label, phase 1, randomized, single center, multiple-dose, 2-period crossover study in 52 healthy adults to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of dexlansoprazole ODT 30 mg as compared to Dexilant delayed-release capsules 30 mg daily for 5 days. The PK parameters on Day 1 and Day 5 are shown below (reproduced from the clinical pharmacology review by Dr. D. Jappara, dated 12/23/2015).

Table 1: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 1 or 5 Days in Healthy Subjects (Reviewer's Analysis)

Parameter	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Day 1: Delayed-Release OD 30 mg Tablet vs. Delayed-Release 30 mg Capsule			
C _{max}	108.51	96.99	121.38
AUC(0-tlqc)	91.81	85.11	99.02
AUC(0-inf)	91.83	85.22	98.95
Day 5: Delayed-Release OD 30 mg Tablet vs. Delayed-Release 30 mg Capsule			
C _{max}	108.57	95.53	123.39
AUC(0-tlqc)	94.90	86.57	104.04
AUC(0-tau)	94.65	86.36	103.73

(source: reproduced from clinical pharmacology review by Dr. D. Jappara, dated 12/23/2015, Table 4, page 9/76)

The 90% confidence intervals (CI) for the dexlansoprazole C_{max}, AUC(0-tlqc), and AUC(0-inf) were all within the 0.80 to 1.25 BE range following single-dose and multiple-dose administration for 5 days. Therefore, the clinical pharmacology reviewers concluded that the data submitted in the NDA demonstrate bioequivalence (BE) between dexlansoprazole ODT 30 mg and Dexilant delayed-release capsule 30 mg. Additionally, following single-dose administration on Day 1 and multiple-dose administration on Day 5, the intragastric pH profile was similar between dexlansoprazole ODT 30 mg and Dexilant delayed-release capsule 30 mg.

The applicant also conducted formulation exploration studies prior to selecting the formulation that was used in the bioequivalence studies. Study TAK-390MR(OD)-102 compared the relative bioavailability of dexlansoprazole for three formulations (X, Y, and Z) of dexlansoprazole delayed-release orally disintegrating tablets. Based on the results of this study, the applicant selected formulation Z as the to-be-marketed formulation. In study TAK-390MR(OD)-102, the AUC from each of the three formulations was equivalent to the AUC of Dexilant delayed-release capsules; however, the C_{max} from the three formulations was higher

than the C_{max} for Dexilant capsules. The clinical pharmacology reviewer concluded that the higher C_{max} observed in study TAK-390MR(OD)-102 is not a concern because 1) bioequivalence was established in Study TAK-390MR(OD)-105, as described previously in this document, 2) an increase in C_{max} of approximately 24% above the C_{max} for Dexilant capsules would not be expected to reduce efficacy; safety is supported by safety data from the approved reference product, Dexilant delay-release capsules at the higher 60 mg strength, and 3) the PK parameters of the selected formulation Z are more consistent with the parameters that passed BE rather than the parameters observed for failed BE. The PK parameters for formulation Z across different studies are shown below.

Table 2: PK Parameters Comparison from Formulation Z of Dexlansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg across Different Studies in Healthy Subjects

Parameters (unit)	103 (food and water effect)	Study 106 (Alternative Dose Administration)	Study 105 Passed BE	Study 102 Failed BE
C_{max} (ng/mL)	688 (48%)	744 (41%)	688 (49)	842 (60)
AUC_{0-t} (ng/mL.h)	2789 (83%)	3011 (67%)	2866 (77%)	3558 (83)
$AUC_{0-\infty}$ (ng•h/mL)	2839 (86%)	3043 (69%)	3048 (78%)	4036 (79)
Median T_{max} (h) [min,max]	4.00 (1.5-6.00)	4.00 (1.50-6.03)	4.00 (1.00-6.00)	4.00 (1.0-7.00)
$T_{1/2}$ (hr)	2.07 (76%)	1.86 (51%)	2.10 (57)	2.01 (50)
CL/F (L/hr)	16.01 (60)	14.02 (63%)	14.24 (58)	11.90 (81%)
Vz/F (L)	47.35 (139)	36.13 (96%)	41.33 (94)	32.7 (121%)

(source: reproduced from clinical pharmacology review by Dr. D. Jappara, dated 12/23/2015, Table 6, page 11/76)

For the reasons described above, the clinical pharmacology reviewer concluded that the selection of formulation Z appears appropriate as the to-be-marketed formulation. Refer to clinical pharmacology review by Dr. D. Jappara for additional details.

Bioequivalence 60 mg strength

Study TAK-390MR(OD)-104 was an open-label, phase 1, randomized, single center, multiple-dose, 2-period crossover study in 52 healthy adults to evaluate the pharmacokinetics and pharmacodynamics of dexlansoprazole following the once daily administration of either two dexlansoprazole ODT 30 mg tablets or one Dexilant 60 mg capsule for 5 days. The clinical pharmacology reviewers determined that two dexlansoprazole ODT 30 mg tablets were not bioequivalent (BE) to one Dexilant 60 mg capsule. The statistical comparisons for the PK parameters are shown below (reproduced from the clinical pharmacology review by Dr. D. Jappara, dated 12/23/2015).

Table 3: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 1 or 5 Days in Healthy Subjects (Reviewer's Analysis)

Parameter	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Day 1: Delayed-Release OD 2 X 30 mg Tablet (Regimen A) vs Delayed-Release 60 mg Capsule (Regimen B)			
C _{max}	92.94	84.41	102.32
AUC(0-tlqc)	75.22	70.15	80.64
AUC(0-inf)	75.71	72.10	84.13
Day 5: Delayed-Release OD 2 X 30 mg Tablet (Regimen A) vs Delayed-Release 60 mg Capsule (Regimen B)			
C _{max}	93.61	84.93	103.18
AUC(0-tlqc)	77.88	70.71	81.1
AUC(0-tau)	78.23	72.55	84.37

(source: reproduced from clinical pharmacology review by Dr. D. Jappar, dated 12/23/2015, Table 9, pages 13-14/76)

Two dexlansoprazole ODT 30 mg tablets and one Dexilant 60 mg capsule meet bioequivalence criteria for C_{max}. However, the AUC of two dexlansoprazole ODT 30 mg tablets is approximately 25% lower on Day 1 and 22% lower on Day 5 than the AUC of one Dexilant 60 mg capsule; the lower 90% CI for AUC was below the 0.80 BE limit on both Day 1 and Day 5.

The clinical pharmacology reviewers explored the potential implication of the differences in AUC on efficacy and safety. Intragastric pH profiles of two dexlansoprazole ODT 30 mg tablets and one Dexilant 60 mg capsule were similar on both Day 1 and Day 5, despite differences in AUC between the two products.

(b) (4)

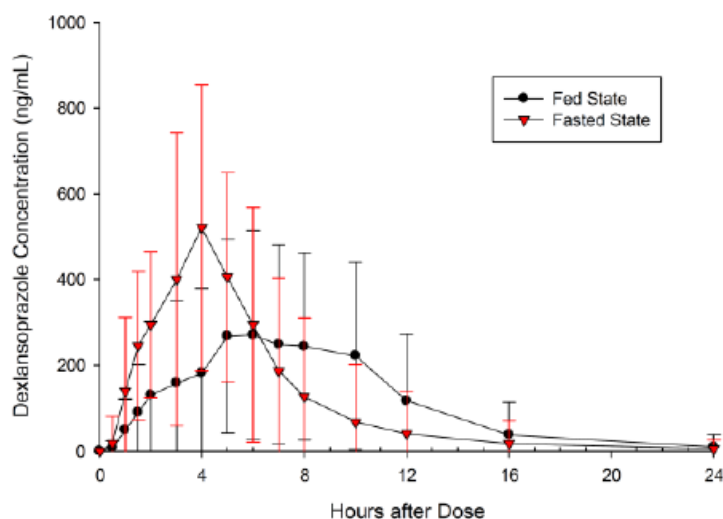
(b) (4)

the clinical pharmacology reviewers. Refer to clinical pharmacology review by Dr. D. Jappar, dated 12/23/2015, for additional details.

Food Effect

The effect of food on dexlansoprazole ODT was evaluated in Study TAK-390MR(OD)-103, an open-label, phase 1, randomized, single-center, single-dose, 3-period crossover study in 72 healthy adults following a single dose administration of dexlansoprazole ODT 30 mg tablets under fed and fasted conditions. When dexlansoprazole ODT 30 mg was administered with a high-fat breakfast,³ the C_{max} decreased by 38% and the t_{max} was delayed by 2 hours, but there was no change to the AUC as compared to the fasted state. The mean plasma concentration-time profiles for dexlansoprazole ODT in the fed and fasted states are shown below.

Figure 1: Mean (SD) Plasma Concentration-Time Profiles for Dexlansoprazole Following Administration of Dexlansoprazole Delayed-Release 30 mg OD Tablet in the Fed and Fasted State in Healthy Subjects



(source: reproduced from clinical pharmacology review by Dr. D. Jappar, dated 12/23/2015, Figure 9, page 18/76)

Exposure-response data or efficacy data from doses lower than the 30 mg dose for the reference product, Dexilant capsules, are not available. In the absence of data to support that the observed reduction in C_{max} would not result in decreased efficacy, the clinical pharmacology reviewers recommend that dexlansoprazole ODT 30 mg tablets be administered at least 30 minutes before a meal.

Water Effect

Study TAK-390MR(OD)-103 also evaluated the effect of water on the pharmacokinetic profile of dexlansoprazole ODT after single administration. As compared to administration without water, the AUC was reduced by 20% and the C_{max} was reduced by 29% when dexlansoprazole ODT 30 mg was administered followed by rinsing the mouth with 240 ml of water. As stated

³ The content of the high-fat, high-caloric breakfast followed the recommendations given in the FDA guidance entitled, "Food Effect Bioavailability and Fed Bioequivalence Studies."

previously, exposure-response data or efficacy data are not available from doses lower than the 30 mg dose for the reference product, Dexilant capsules, to support that the reduction in AUC by 20% and reduction in C_{max} by 29% would not result in decreased efficacy. Therefore, the clinical pharmacology reviewers recommend the following for the administration instructions:

- Dexlansoprazole ODT 30 mg should be placed on the tongue, allowed to disintegrate, and the microgranules should be swallowed without water.

Alternative Options for Dose Administration

Study TAK-390MR(OD)-106 was an open-label, randomized, single-center, single-dose, 4-period cross-over study in 71 healthy adults to assess pharmacokinetics and relative bioavailability for three alternative options for administration (i.e., orally via syringe, via nasogastric tube, swallowed intact with water). When a dexlansoprazole ODT 30 mg tablet was mixed with water and administered via an oral syringe, via a nasogastric (NG) tube, or swallowed as an intact tablet with water, each method of administration was found to be bioequivalent to the oral administration of the intact/whole tablet on the tongue, allowed to disintegrate, and swallowed without water. The statistical comparisons of pharmacokinetic estimates for alternative dose administration options are shown below.

Table 4: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Administration of Dexlansoprazole Delayed- Release OD 30 mg Tablet as an Aqueous Mixture via an Oral Syringe or NG Tube, as the Intact Tablet Swallowed with Water, or as the Intact Tablet on the Tongue without Water in Healthy Subjects (clinical pharmacology reviewer's analysis)

Parameter (N)	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Oral Syringe Administration (Regimen A) vs Intact Tablet on the Tongue (Regimen D)			
C_{max}	101.92	93.02	111.67
AUC(0-tlqc)	100.71	94.12	107.76
AUC(0-inf)	100.72	94.18	107.71
NG Tube Administration (Regimen B) vs Intact Tablet on the Tongue (Regimen D)			
C_{max}	106.61	97.25	116.88
AUC(0-tlqc)	108.46	101.32	116.09
AUC(0-inf)	108.34	101.24	115.95
Intact Tablet Swallowed With Water (Regimen C) vs Intact Tablet on the Tongue (Regimen D)			
C_{max}	101.099	92.33	110.70
AUC(0-tlqc)	101.892	95.28	108.96
AUC(0-inf)	102.29	95.68	109.37

(source: reproduced from clinical pharmacology review by Dr. D. Jappar, dated 12/23/2015, Table 20, page 23/76)

Based on the results of Study TAK-390MR(OD)-106, the clinical pharmacology reviewers recommend that dexlansoprazole ODT 30 mg tablets can be administered with water via oral syringe, NG tube, or swallowed whole with water.

Disintegration Time

The in-vivo disintegration time for dexlansoprazole ODT 30 mg tablets was evaluated in Study TAK-390MR(OD)-107 in 8 healthy adults. The in-vivo disintegration time on the tongue was found to be a mean of 36 seconds (range 29-43 seconds). In this study, the subjects swallowed 20 ml of spring water 30 seconds prior to administration of the study drug, which may

decrease the disintegration time; therefore, the clinical pharmacology reviewers noted that the findings in this study may be unreliable since subjects were allowed to drink water. Of note, this study focused on the in-vivo disintegration time, whereas, the disintegration time described in the current Guidance for Industry: Orally Disintegrating Tablets⁴ recommends an in-vitro disintegration time. The in-vivo disintegration time reported is similar to the in-vitro disintegration time of (b) (4) seconds (95% CI: (b) (4) seconds). In the primary BE study to support product labeling, dexlansoprazole ODT 30 mg was administered on the tongue, allowed to disintegrate, and swallowed without water and without chewing, which is consistent with the general definition of an orally disintegrating tablet. In this study, dexlansoprazole ODT 30 mg was found to be bioequivalent to Dexilant capsule 30 mg. Therefore, the clinical pharmacology reviewers concluded that the reported in-vivo disintegration time will not have implications for labeling.

Alcohol Dose Dumping

An in-vitro alcohol dose dumping study demonstrated potential for alcohol dose-dumping at the acid stage in the presence of 40% alcohol. Ninety percent of the drug was released within 30 minutes in the presence of 40% alcohol as compared to 1-2% drug release at the same time point in the presence of 0%, 5%, and 20% alcohol. The clinical pharmacology reviewers concluded that the observed alcohol dose dumping could potentially shorten the t_{max} and reduce AUC and C_{max} by exposing the acid-labile drug early in the acidic environment of the stomach, thereby potentially decreasing efficacy. Since the reviewers did not anticipate that the alcohol dose dumping would affect the safety profile of the drug, further in-vivo alcohol dose dumping studies were not recommended; however, this issue should be addressed in the label to recommend avoidance of alcohol when taking dexlansoprazole ODT.

Site Inspection

An inspection was requested for the clinical and bioanalytical sites that conducted the primary bioequivalence studies to support product labeling (i.e., study TAK-390MR(OD)_105 and study TAK-390MR(OD)_104). However, the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended on 06/12/2015 that data could be accepted without an on-site inspection because the sites that conducted these two studies were recently inspected with a classification of No Action Indicated (NAI).

For a detailed review of the clinical pharmacology data provided in this NDA, refer to the clinical pharmacology review by Dr. D. Jappara (primary review), and Drs. S. Lee and Dr. H. Ahn (secondary reviewers), dated 12/23/2015. The clinical pharmacology reviewers have not recommended PMCs or PMRs. The final labeling includes recommended changes by the clinical pharmacology reviewers.

⁴ Guidance for Industry: Orally Disintegrating Tablets, December 2008. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf>

5) Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because dextansoprazole ODT is not intended as an antimicrobial product.

6) Clinical/Statistical- Efficacy

No clinical efficacy studies were conducted as part of this NDA submission.

7) Safety

Dexilant (dextansoprazole) delayed-release orally disintegrating tablets (ODT) contains the same active moiety, dextansoprazole, as Dexilant delayed-release capsules, approved January 30, 2009 (NDA 022287). In this section, dextansoprazole ODT will be referred to as dextansoprazole ODT, or ODT; Dexilant delayed-release capsules will be referred to as Dexilant capsules, or capsules. The applicant evaluated dextansoprazole ODT in seven phase 1 studies in healthy adults, conducted in the United States, which were completed by November 2014. The studies were conducted in accordance with the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and local requirements. This safety analysis combines six of the phase 1 studies, which enrolled 365 healthy subjects who received at least 1 dose of dextansoprazole ODT. One study, study TAK-390MR(OD)_107, is not included in this pooled safety analysis since the objective of study TAK-390MR(OD)_107 was to examine the in-vivo dissolution of dextansoprazole ODT and the granules were not swallowed. Furthermore, no adverse events were reported during Study TAK-390MR(OD)_107. The studies included in the safety analyses are summarized in Table 5 below.

Table 5: Summary of Studies included in Pooled Safety Analyses

Study Number (No. of Subjects)	Dexlansoprazole OD Tablet Doses Evaluated (QD)	Comparator (a) (QD)	Treatment Duration	Evaluation (Study Type)
Phase 1 Pooled Studies				
TAK-390MR (OD)_101 (N=48)	OD tablet Formulation A (30 mg) OD tablet Formulation B (30 mg)	30 mg capsule	Periods 1-3: 5 days separated by a minimum of 5 days WO Period 4: 1 day after a minimum of 5 days WO following Period 3	Bioavailability and intragastric pH response to OD tablets (PK/bioavailability and safety)
TAK-390MR (OD)_102 (N=64)	30 mg OD tablet Formulations X, Y, and Z (b)	30 mg capsule	1 day in each of 4 periods, separated by a minimum of 5 days WO	Bioavailability of OD tablets (Bioequivalence and safety)
TAK-390MR (OD)_103 (N=72)	30 mg OD tablet	None	1 day in each of 3 periods, separated by a minimum of 5 days WO	Food effect study and effect of water rinse after administration (Bioavailability and safety)
TAK-390MR (OD)_104 (N=52)	2×30 mg OD tablet	60 mg capsule	5 days in each of 2 periods, separated by a minimum of 7 days WO	Bioavailability and intragastric pH response to OD tablets (PD/bioavailability and safety)
TAK-390MR (OD)_105 (N=52)	30 mg OD tablet	30 mg capsule	5 days in each of 2 periods, separated by a minimum of 7 days WO	Bioavailability and intragastric pH response to OD tablets (PK/PD/bioavailability and safety)
TAK-390MR (OD)_106 (N=77)	30 mg OD tablet	None	1 day in each of 4 periods, separated by a minimum of 5 days WO	Bioavailability of OD tablets administered without water, swallowed intact with water, or mixed with water and administered orally via syringe or via NG tube (Bioavailability and safety)

NG=nasogastric, PD=pharmacodynamics, PK=pharmacokinetics, QD=once daily, WO=washout.

(a) Comparator = dexlansoprazole capsules.

(b) Formulation Z was chosen for further development.

(source: applicant's NDA 208056 submission, module 2.7.4 Summary of Clinical Safety, page 5/25)

The safety data from the six phase 1 studies were pooled into an integrated safety database by the applicant. Disposition, demographics, and adverse events were summarized by treatment received, dexlansoprazole capsules, dexlansoprazole ODT, or combined dexlansoprazole capsules and ODT. The subjects were administered the following doses depending on the study, as described above in Table 5: dexlansoprazole ODT 30 mg, dexlansoprazole ODT 30 mg x 2, dexlansoprazole capsules 30 mg, and dexlansoprazole capsules 60 mg.

Three-hundred sixty-five subjects were treated with the ODT and/or capsules. Of the 365 subjects, 313 subjects received dexlansoprazole 30 mg ODT, 52 subjects received two 30 mg ODT (2 x 30 mg ODT), 160 subjects received dexlansoprazole 30 mg capsules, and 52 subjects received dexlansoprazole 60 mg capsules. Subjects who received treatment in more than one group are included under each treatment received.

In the dexlansoprazole ODT group, 92/365 (25%) subjects experienced 189 adverse events. In the capsule group, 48/212 (23%) subjects experienced 66 adverse events. Overall, the adverse events were either considered as not related to the study drug and were mild or moderate. There were no deaths, no serious adverse events, and no severe adverse events were reported.

Exposure

The overall exposure by treatment group (described as: OD Tablets 30 mg, OD Tablets 30 mg x 2, capsule 30 mg, capsule 60 mg) is shown below in Table 6. The maximal exposure to dexlansoprazole during these phase 1 studies was 16 days with a maximum exposure to dexlansoprazole ODT of 11 days.

Table 6: Overall Exposure by Treatment Group: Pooled Safety Analysis

Duration (days)	Dexlansoprazole Treatment Group			
	OD Tablet 30 mg N=313 PY=4.0	OD Tablets 2x30 mg N=52 PY=0.7	Capsule 30 mg N=160 PY=1.5	Capsule 60 mg N=52 PY=0.7
Mean (SD)	4.7 (2.80)	5 (0)	3.5 (1.95)	5 (0)
Median	4.0	5.0	5.0	5.0
Min-Max	1 – 11	5 – 5	1 – 5	5 – 5
Incremental Exposure N (%)				
≤1 day	8 (2.6)	0	62 (38.8)	0
2 to <7 days	257 (82.1)	52 (100.0)	98 (61.3)	52 (100.0)
7 to <14 days	48 (15.3)	0	0	0
≥14 days	0	0	0	0
Cumulative Exposure N (%)				
≥1 day	313 (100.0)	52 (100.0)	160 (100.0)	52 (100.0)
≥7 days	48 (15.3)	0	0	0
≥14 days	0	0	0	0

PY= patient-years.

(source: applicant's NDA 208056 submission, module 2.7.4 Summary of Clinical Safety, page 9/25)

Overall, the exposure is sufficient for the purposes of conducting phase 1, bioequivalence and bioavailable studies in healthy subjects.

Disposition and Discontinuations

Overall, the demographic distribution between subjects treated with dexlansoprazole ODT and dexlansoprazole capsules was numerically similar. The majority of subjects were Caucasian (283/365 [77.5%]), and the age of subjects in the phase 1 studies ranged from 19 to 55 years of age, with a median age of 36 years. The proportion of males (213/365 [58.4%]) enrolled in the studies was higher than the proportion of females (152/365 [41.6%]). However, there were no imbalances in the demographic distribution that would be expected to impact the results of these phase 1 bioequivalence/bioavailability studies.

Three-hundred forty-five out of three-hundred sixty five (94.5%) subjects completed treatment with dexlansoprazole ODT and 211/212 (99.5%) subjects completed treatment with dexlansoprazole capsules. A higher proportion of subjects treated with dexlansoprazole ODT discontinued the study drug [20/365 [5%]] as compared to subjects treated with capsules

(1/212 [0.5%]). Of the 21 subjects who discontinued from the studies, 8 subjects withdrew because of adverse events, 3 subjects withdrew consent, 1 subject withdrew due to attending a funeral, 1 withdrew due to job requirements, 1 subject's reason as unknown, 1 subject did not return after the period 4 visit, 1 subject did not return for period 2 of the study, and 5 subjects discontinued due to a positive drug test. The subjects who discontinued due to adverse events are discussed below.

Study Discontinuations due to Adverse Events

There were 8 subjects who discontinued the study drug due to adverse events, 7 subjects were in the ODT group and 1 subject was in the capsule group. The subject in the capsule group (Study TAK-390MR(OD)_101) withdrew due to elevated alanine aminotransferase (ALT) with onset 16 days after completing treatment; a normal ALT value was noted at the day 67 follow up visit. The other adverse events that led to study withdraw were reported the ODT group in the following studies:

- Study TAK-390MR(OD)_102
 - o One subject with decreased absolute neutrophil count on day 7 that resolved on day 21.
- Study TAK-390MR(OD)_103
 - o One subject with pressure of speech and agitation after one dose of the study drug,
 - o One subject with anemia at baseline and continued to have anemia that was considered to be related to phlebotomy,
 - o One subject with anxiety, dysphonia, oropharyngeal pain, and throat tightness after one dose of the study drug, and was withdrawn on day 19. This subject was sent to the hospital and developed dizziness, headache, hyperhidrosis, pallor, visual impairment, decreased oxygen saturation, tremor, dyspnea, nausea, vomiting, asthenia, and became unresponsive to stimuli. The subject was discharged after several hours in a local emergency room, but the medical records indicated that the subject had prior conditions that were not disclosed during the screening period, including leukodystrophy, supraventricular tachycardia, tricuspid valve incompetence, and migraines. A diagnosis was not provided by the hospital but the applicant notes that all laboratory findings, ECG, and physical exam were normal during the study, and that all events were resolved.
- Study TAK-390MR(OD)_105
 - o One subject with elevated CPK and elevated AST and ALT. The subject narrative is provided below.
- Study TAK-390MR(OD)_106
 - o One subject with elevated CPK (narrative is provided below),
 - o One subject with nasal discomfort, likely related to placement of the nasogastric (NG) tube.

Three of the adverse events that led to study drug discontinuation were considered as related: 1 subject in the ODT group with oropharyngeal pain and throat tightness, 1 subject in the capsule group with elevated ALT, 1 subject in ODT group with anemia, considered as related to phlebotomy during the trial, and 1 subject in the ODT group with nasal discomfort after

insertion of a NG tube. All of these events had an outcome of resolved or recovered except for one subject in Study 103 who experienced pressure of speech and agitation; the outcome was “unknown.” This subject had a vague history of mental illness and received one dose of the study drug on day 1; therefore, given the exposure to only one dose of the study drug and the potential confounding conditions, the event is likely unrelated to the study drug.

Elevated blood creatine phosphokinase (CPK)

Elevated blood creatine phosphokinase (CPK) occurred in 2 subjects, both of whom were treated with the ODT formulation. Elevated creatine phosphokinase (CK) is not described in the approved label for Dexilant capsules or the racemate, lansoprazole; however, elevated creatine kinase is described in the label for another proton pump inhibitor, pantoprazole.⁵ Since elevated creatine phosphokinase is not currently described in the Dexilant label and occurred in 2/365 (0.5%) subjects who received the ODT and in none of the subjects who received the capsule, this reviewer evaluated these events in further detail to determine whether a labeling change was warranted.

The narratives are provided below for the two subjects who experienced elevated CPK.

- One subject in Study TAK390MR(OD_105), a 32 year old male, experienced an adverse event of elevated serum CK beginning on Day 11, five days after the last administration of the study drug. The subject received 5 doses of the ODT formulation (Regimen A) from Day 1 to Day 5 and did not receive the capsule formulation (Regimen B). The CK on Day -1 was 112 U/L; however, the CK was found to be elevated at 20,789 U/L, 25,803 U/L, and 3813 U/L on Days 11, 12, and 15 (early termination visit), respectively. The CK returned to a normal value of 140 U/L on Day 25 at the follow-up visit. Of note, the ALT and aspartate aminotransferase (AST) values were also elevated on Day 11 at 64 U/L and 188 U/L, respectively. On Days 12 and 15, ALT values remained elevated at 100 U/L and 103 U/L, and AST values were elevated at 275 U/L and 85 U/L. On Day 25, both ALT and AST returned to normal with values of 35 U/L and 21 U/L, respectively. The applicant notes that the ALT was not >3 times the upper limit of normal (ULN), bilirubin was within normal limits, and it was believed that the changes were probably related to exercise. No additional adverse events were reported for this subject and physical examination and ECG were all within normal limits. In the applicant’s response to an Information Request, dated September 24, 2015, the applicant noted that on both Days 1 and 5, the dexlansoprazole plasma concentration was below the limit of qualification; suggesting little to no accumulation of the study drug after 5 days of administration of 30 mg ODT. The subject was withdrawn from the study on Day 25 due to the event of elevated CK, which resolved. The investigator considered this event to be mild in intensity and not related to study medication.
- One subject in Study TAK390MR(OD_106), a 42 year old male, experienced an adverse event of elevated serum CK beginning on Day 18, five days after the most recent dose of study drug. The subject was withdrawn from the study due to the event.

⁵ Protonix approved label, last revised on 12/19/2014, available at:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022020s011-020987s049lbl.pdf

On Day -1 of Period 1, the CK was 112 U/L, within the normal range of 0-360 U/L. On Day 18, the CK was elevated at 761 U/L and continued to be elevated on Day 19 (early termination visit) at 797 U/L. On Day 79 (unscheduled visit), the CK value was normal at 106 U/L. There were no concomitant medications reported, no clinically significant ECG findings, no abnormal vital signs, and the physical examination was normal with no clinically significant changes from baseline. In the applicant's response to an Information Request, dated September 24, 2015, the applicant noted that the dexlansoprazole plasma concentration was below the limit of qualification at 16 hours post-dose; suggesting little to no accumulation of the study drug. There was no other information available to further inform this event.

Based on the review of the information provided in the submission and in response to the Information Request, it is difficult to make definitive conclusions on the relationship of the event to the study drug. Of note, there are also two reports of elevated CK in the postmarketing safety update reports (PSUR) from 2010 and 2011 for subjects who were administered Dexilant 60 mg capsules. Both events had limited available information to allow for causality determinations. Therefore, given the small number of cases (i.e., 2 subjects administered dexlansoprazole ODT in phase 1 trials) and the short duration of exposure in the phase 1 studies, this reviewer does not recommend that these events be added to the label at this time since available data are insufficient to allow for definitive conclusions on causality. If additional data become available to suggest causality between dexlansoprazole and elevated CK, the implications for labeling will be considered at that time. Of note, the applicant agreed to continue to monitor CK elevation as part of the routine Pharmacovigilance activities.

Deaths and Serious Adverse Events

No deaths or serious adverse events were reported during the phase 1 studies.

Treatment-Emergent Adverse Events (TEAEs)

Of the three-hundred sixty-five subjects, 119 (32.6%) subjects reported at least one treatment-emergent adverse event (TEAE). The most common TEAEs included headache, nausea, constipation, vessel puncture site pain, and oropharyngeal pain. The table below summarizes the TEAEs that occurred in $\geq 1\%$ of subjects in the 6 pooled phase 1 studies.

Table 7: Treatment-Emergent Adverse Events that Occurred in at least 3 ($\geq 1\%$) of Subjects in the 6 pooled phase 1 studies where dexlansoprazole orally disintegrating tablet (ODT) > dexlansoprazole delayed-release capsule

Treatment Emergent Adverse Event (TEAE)	ODT N= 365 n (%)	Capsule N= 212 n (%)
Headache	25 (6.8)	14 (6.6)
Vessel Puncture Site Pain	8 (2.2)	2 (0.9)
Constipation	5 (1.4)	2 (0.9)
Nausea	5 (1.4)	2 (0.9)
Arthropod Bite	4 (1.1)	0.0
Back Pain	4 (1.1)	0.0
Erythema	4 (1.1)	2 (0.9)
Excoriation	4 (1.1)	2 (0.9)
Pruritus	4 (1.1)	2 (0.9)
Dizziness	3 (0.8)	0.0
Rhinorrhea	3 (0.8)	0.0
Vomiting	3 (0.8)	0.0

Note that subjects who received more than one formulation are counted in each of treatment groups for the formulation received. (source: reviewer's analysis, created using applicant's data in NDA 208056 submission, module 5.3.5.3, Data Analysis Dataset "adae")

This reviewer conducted her own analysis using the applicant's data (applicant's NDA 208056 submission, module 5.3.5.3, Data Analysis Dataset "adae") and confirms the applicant's findings presented in module 2.7.4 Summary of Clinical Safety.

Overall, the adverse events reported by subjects who received the ODT were numerically similar to those reported by subjects who received the Dexilant capsules. The adverse events reported during the phase 1 trials are either included in the Dexilant label or considered as unrelated to the study drug (e.g., arthropod bite, vessel puncture site pain). The currently approved label for Dexilant delayed-release capsules⁶ lists the adverse reactions that occurred in $\geq 2\%$ and higher than placebo. In general, other than headache and vessel puncture site pain, the adverse events reported during the phase 1 trials occurred at a lower frequency than in the controlled trials that supported product labeling for Dexilant capsules. Since the TEAEs were overall numerically similar between the groups and the studies were conducted in healthy subjects with short duration of exposure to dexlansoprazole, no changes are recommended to Section 6 of the label at this time.

Treatment-Emergent Adverse Events (TEAEs) by Dose and Formulation

In addition, to evaluate adverse events by dose and formulation, this reviewer conducted analyses using the applicant's pooled safety analysis dataset (applicant's NDA 208056 submission, module 5.3.5.3, Data Analysis Dataset "adae"). The analyses are summarized below in Table 8.

⁶ Dexilant delayed-release capsule, approved label, last revised on 12/19/2014, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022287s019lbl.pdf

Table 8: Treatment-Emergent Adverse Events that Occurred at the dexlansoprazole 30 mg dose (ODT and Capsule) and where ODT $\geq$ Capsule

TEAE	ODT 30 mg N= 313 n (%)	Capsule 30 mg N = 160 n (%)
Headache	22 (7.0)	6 (3.8)
Vessel Puncture Site Pain	7 (2.2)	1 (0.6)
Constipation	5 (1.6)	2 (1.3)
Pruritus*	5 (1.5)	1 (0.6)
Rash*	4 (1.3)	1 (0.6)
Erythema	4 (1.3)	1 (0.6)
Oropharyngeal Pain	4 (1.3)	1 (0.6)
Nausea	2 (0.6)	1 (0.6)
Vessel Puncture Site Swelling	2 (0.6)	1 (0.6)

*Note: Pruritus includes pruritus and pruritus generalized. Rash includes rash, rash papular, and rash macular. (source: reviewer's analysis using conducted using the applicant's data, NDA 208056 submission, module 5.3.5.3, Data Analysis Dataset "adae")

Overall, the type of TEAEs that occurred were similar between the 30 mg ODT and 30 mg capsule groups; only headache and vessel puncture site pain occurred at a higher frequency in subjects who received the ODT as compared to subjects who received the capsules. The other TEAEs occurred at numerically similar frequencies between the two groups.

In Table 8 above, headache occurred more frequently in the ODT 30 mg group (22 subjects, 7.0%) as compared to the capsule 30 mg group (6 subjects, 3.8%). In contrast, when 2 x 30 mg ODT are compared to 60 mg capsule, headache was reported in a lower proportion of subjects in the 2 x 30 mg ODT group as compared to the 60 mg capsule group (3 [5.8%] subjects vs. 8 [15.4%] subjects). When the ODT and capsules groups are combined, the overall proportion of subjects experiencing headache is similar (approximately 7% each). Furthermore, the medical officer clinical review of the trials that supported product labeling for Dexilant capsules (NDA 22287), by Dr. T. Johnson,⁷ states that headache occurred more frequently in the placebo group (38/260 subjects [4%]) as compared to the Dexilant 30 mg dose arm (16/175 subjects [2%]) and Dexilant 60 mg dose arm (79/874 [1.5%]).

Although headache occurred more frequently in the ODT 30 mg group as compared to the capsule 30 mg group in the phase 1 trials evaluating dexlansoprazole ODT, healthy subjects may report AEs differently than subjects with the disease, and overall, the proportion of subjects reporting headache was numerally similar between the ODT and capsule groups. Furthermore, in the phase 3 trials that supported product labeling, headache was reported more frequently in the placebo group as compared to the Dexilant-treated group(s). Therefore, this reviewer concludes that a change to the label is not necessary at this time.

In addition to headache and vessel puncture site pain occurred more frequently in the ODT 30 mg group as compared to the capsule 30 mg group (8/365 [2%] subjects vs. 2/212 [1%])

⁷ Medical officer clinical review, NDA 22287, Dexilant delayed-release capsules, approved on 1/30/2009, available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022287s000_MedR_P1.pdf

subjects); however, this reviewer concludes that this TEAE is not related to the study drug, instead it is likely related to the blood draw procedure.

Of note, oropharyngeal pain is not described in the currently approved Dexilant label; however, this TEAE occurred in a numerically similar proportion of subjects treated with ODT and capsules (approximately 1% each). Therefore, a change to the label is not recommended at this time.

This reviewer also compared TEAEs for subjects who received 2 x 30 mg ODT vs. subjects who received 60 mg capsules. For subjects who received 2 x 30 mg ODT, the TEAEs that occurred in at least 2 subjects included headache in 3 (5.8%) subjects, nausea in 3 (5.8%) subjects, and flatulence in 2 (3.8%) subjects. In the subjects who received 60 mg capsules, TEAEs that occurred in at least 2 subjects included headache in 8 (15.4%) subjects, decubitus ulcer in 3 (5.8%) subjects, and oropharyngeal pain in 2 (2.8%) subjects. The nature of the TEAEs varied between the groups, no new or unexpected adverse events were identified from the phase 1 studies, and no notable differences were observed between 2 x 30 mg ODT vs. 60 mg capsules.

Overall, with the exception of headache, TEAEs occurred in a small number of subjects and there were no meaningful differences observed between the dexlansoprazole ODT and dexlansoprazole capsules during the phase 1 studies. In general, the adverse events reported during the pooled phase 1 studies are consistent with the known safety profile of Dexilant delayed-release capsules.

8) Advisory Committee Meeting

No advisory committee was held for review of this application.

9) Pediatrics

The Division consulted the Division of Pediatric and Maternal Health (DPMH) to aid in the review of the labeling. The reader is referred to the DPMH consultation review, by Dr. A. Taylor, dated 12/20/2015, for further details. The DPMH recommendations have been incorporated into the final labeling.

PREA Requirements

The sponsor submitted an iPSP on May 29, 2014. The Division reviewed the iPSP and discussed the recommendations with PeRC on August 6, 2014. Since dexlansoprazole is currently not approved in any pediatric age group, the Division recommended that the iPSP be revised to indicate that the applicant plans to conduct required studies under PREA for dexlansoprazole ODT. The Division acknowledged that the applicant may, upon review, be able to rely on data from the planned/ongoing safety and efficacy trials of dexlansoprazole capsules in pediatric patients to fulfill the required pediatric assessments for dexlansoprazole ODT. The applicant revised the iPSP to be consistent with the recommendations made by the

Division and the PeRC, and submitted an Agreed iPSP, dated November 19, 2014. The applicant received confirmation of agreement on the Agreed iPSP, dated December 11, 2014.

The following PREA studies are required under Dexilant delayed-release capsule NDA 22287.

Infants 1 to 11 months of age

- 1788-2 Deferred study under PREA to evaluate the pharmacokinetic, pharmacodynamic, and safety profiles of dextansoprazole in patients ages 1 month to 11 months of age with endoscopy-proven erosive esophagitis (EE).
- 1788-4 Deferred study under PREA to evaluate the long-term safety of dextansoprazole for the healing and maintenance of healing of EE in pediatric patients 1 month to 11 months of age who require chronic treatment with dextansoprazole due to underlying conditions that predispose to chronic GERD and EE.

Children 1 to 11 years of age

- 1356-4 Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 to 11 years.
- 1788-3 Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven EE in patients aged 1 to 11 years.

Adolescents 12 to 17 years of age

- 1356-5 Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 to 17 years.
- 1788-1 Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven EE in patients aged 12 to 17 years of age.

Long-term Safety Study in Pediatric Patients 1 to 17 years of age

- 1788-5 Deferred study under PREA to evaluate the long-term safety of dextansoprazole for the healing and maintenance of healing of EE in pediatric patients 1 to 17 years of age who require chronic treatment with dextansoprazole due to underlying conditions that predispose them to chronic GERD and EE.

In this NDA, the applicant requested a deferral for pediatric studies in pediatric patients ages 1 to 17 years of age for all indications, and a deferral for pediatric patients 1 month to 11 months old (b) (4) maintaining healing of EE (b) (4). A waiver request was submitted for studies in pediatric patients 1 to 11 months of age for the indication of treatment of heartburn associated with symptomatic non-erosive GERD, and for patients 0 to 1 month for all indications. No changes have been made to the pediatric program since the Agreed iPSP, dated December 11, 2014. The pediatric plan was presented to PeRC on December 9, 2015. PeRC generally agreed with the approach outlined in the agreed iPSP but recommended that the timeline for submission of required pediatric studies under this NDA (NDA 208056) be shortened.

Proposed Pediatric Study Request (PPSR)

The applicant submitted a PPSR, dated April 3, 2015, and included the indications and pediatric age groups below:

(b) (4)

(b) (4) Maintaining healing of EE and relief of heartburn in pediatric patients 1 to 11 months of age and 12 to 17 years of age.
Treatment of heartburn associated with symptomatic non-erosive GERD in pediatric patients 1 to 17 years of age.

The applicant did not include studies in pediatric patients 1 year to 11 years of age for the healing of EE and maintaining healing of EE and relief of heartburn because the studies were not expected to be completed in time to benefit from pediatric exclusivity. As a result, an Inadequate Letter was issued, dated July 21, 2015. The letter recommended that the applicant include the 1 year to 11 year age group and also suggested that studies for the treatment of *Helicobacter pylori* be included in the PPSR. The applicant was also encouraged to submit the completed studies in adolescent patients for review, even though a Written Request (WR) had not been issued; however, the applicant was informed that these studies would not be included in the WR. Of note, an efficacy supplement was submitted to Dexilant capsule NDA 22287 on September 30, 2015, including the results of trials conducted using the Dexilant delayed-release capsules in adolescent patients 12 to 17 years of age to support product labeling for same indications as approved in adults. The efficacy supplement is currently under review by the Division with a PDUFA goal date of July 30, 2016. If all indications are expanded to include adolescent patients 12 to 17 years of age, this efficacy supplement would fulfill the PREA requirements 1356-5 and 1788-1, described above.

The PREA requirements and timeline for submission are described below in Section 12 of this document. For final agreements, refer to the approval letter for this NDA.

10) Other Relevant Regulatory Issues

Regulatory Action

The data provided in the NDA submission failed to demonstrate bioequivalence between two dexlansoprazole ODT 30 mg tablets and one Dexilant delayed-release capsule 60 mg;

(b) (4)

The reader is referred to the Approval Letter for the final recommendations that were communicated to the applicant.

Financial Disclosures

The applicant stated that no investigator or sub-investigator entered into any financial arrangement whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), nor did any investigator or sub-investigator disclose financial interests/arrangements. Therefore, there are no issues surrounding the approvability of the application or questions about the data integrity since there were no investigators with disclosed financial interests, nor did any investigator receive significant payments of other sorts as defined in 21 CFR 54.2(f).

11) Labeling

Proprietary Name

The Office of Medication Error Prevention and Risk Management determined that the proposed proprietary name “Dexilant SoluTab” is acceptable. The reader is referred to the Proprietary Name review by Drs. S. Abraham, K. Worthy, and L. Merchant, dated 7/19/2015.

Specific Labeling Issues

Multiple labeling negotiations occurred between the applicant and the review team during the review cycle, and were ongoing at the time of this document. For final labeling agreements, the reader is referred to the approved product label. The key changes to the labeling available at the time of this review are summarized below.

Information on dexlansoprazole ODT is proposed to be added to the approved label for Dexilant delayed-release capsules. The label was revised throughout to specify data generated from studies conducted with Dexilant delayed-release capsules vs. data from studies conducted with dexlansoprazole ODT.

Highlights

- Information was added to include indication statements, administration instructions for dexlansoprazole ODT.

Section 1 Indications and Usage

- The approved indications for Dexlansoprazole ODT were added to the currently approved indications for Dexilant delayed-release capsules, including maintaining of healing of erosive esophagitis and relief of heartburn, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

Section 2 Dosage and Administration

- Section 2.1 was revised to include dosage recommendations, described in separate tables for Dexilant delayed-release capsules and dexlansoprazole ODT, (b) (4)
- Section 2.2 was revised to describe the dosage adjustment in patients with hepatic impairment.
- Section 2.3 was revised to include separate administration instructions for dexlansoprazole ODT.

Section 7 Drug Interactions

- A table was added to describe clinically relevant interactions affecting drugs co-administered with Dexilant (b) (4)

Section 8 Use in Specific Populations

- Section 8.1 was updated to include the text summarizing the animal data (b) (4)
- (b) (4)
- (b) (4) Section 8.6 Hepatic Impairment. The language was revised to describe recommendations for use in patients with hepatic impairment.

Section 12 Clinical Pharmacology

- The section was revised to be consistent with the Clinical Pharmacology Labeling Guidance.
- Clinical pharmacology data relevant to dexlansoprazole ODT was added throughout the section.

Section 13 Nonclinical Toxicology

- (b) (4)

Section 14 Clinical Studies

- A general statement was added to clarify that dexlansoprazole ODT is not recommended for the healing of EE indications (b) (4)

In addition to the review team and DPMH consultants, the labeling was also reviewed by the Division of Medical Error Prevention and Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP). Their comments and recommendations have been incorporated into the final labeling. Labeling negotiations were ongoing at the time of this document. For final labeling agreements, the reader is referred to the approved product label.

12) Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend that dexlansoprazole ODT 30 mg be approved for the following indications:

- Maintaining healing of erosive esophagitis and relief of heartburn.
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

(b) (4)
the data provided failed to establish bioequivalence between two dexlansoprazole ODT 30 mg and one Dexilant delayed-release capsule 60 mg.

Risk Benefit Assessment

In support of this NDA, the applicant conducted seven phase 1 studies (6 bioavailability/bioequivalence [BA/BE] studies and 1 in-vivo disintegration time study) in healthy adults to support the proposed indications. No additional clinical efficacy or safety trials evaluating the dexlansoprazole ODT formulation were conducted and submitted in this NDA.

I agree with the reviewers that the data submitted in the NDA establish BE between dexlansoprazole ODT 30 mg and Dexilant delayed-release capsule 30 mg. The 90% confidence intervals (CI) for the dexlansoprazole C_{max} , AUC(0-t_{lqc}), and AUC(0-inf) were all within the 0.80 to 1.25 BE range following single-dose and multiple-dose administration for 5 days. However, two dexlansoprazole ODT 30 mg tablets did not meet the criteria for BE when compared to one Dexilant delayed-release capsule 60 mg. Two dexlansoprazole ODT 30 mg and one Dexilant delayed-release capsule 60 mg demonstrate equivalence for C_{max} ; however, the AUC of two dexlansoprazole ODT 30 mg tablets is approximately 25% and 22% lower than that of Dexilant 60 mg capsule on day 1 and day 5, respectively. The lower 90% CI for AUC was below the 0.80 BE limit on both day 1 and day 5.

Despite the difference in AUC, the intragastric pH profiles were similar on both day 1 and day 5. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The adverse event profile was generally comparable between dexlansoprazole ODT and Dexilant capsules based on the adverse events reported during the pooled phase 1 studies, and were consistent with the known safety profile of Dexilant capsules.

Based on the totality of the data, I agree with the reviewers that dexlansoprazole ODT 30 mg should be approved for the indications of maintaining healing of erosive esophagitis and relief of heartburn, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease based on the establishment of bioequivalence between dexlansoprazole ODT 30 mg and Dexilant capsule 30 mg. (b) (4)

ata provided failed to establish bioequivalence between two dexlansoprazole ODT 30 mg and one Dexilant delayed-release capsule 60 mg. Additionally, I had no disagreements with the conclusions or recommendations from any of the review disciplines involved with this NDA.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS is not recommended.

Recommendation for other Postmarketing Requirements and Commitments

The following post-marketing requirements (PMRs) and timelines are being negotiated at the time of this review. For final agreements, refer to the Approval Letter.

PREA PMRs

- 1) Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 year to 11 years
 - a. Final Protocol Submission Date: October 2020
 - b. Study/Trial Completion Date: October 2024
 - c. CSR Submission Date: October 2025
- 2) Deferred study under PREA to evaluate the pharmacokinetics, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 1 year to 11 years of age.
 - a. Final Protocol Submission Date: October 2020

- b. Study/Trial Completion Date: October 2024
 - c. CSR Submission Date: October 2025
- 3) Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 year to 17 years.
- a. Final Protocol Submission Date: October 2016
 - b. Study/Trial Completion Date: October 2018
 - c. CSR Submission Date: October 2020
- 4) Deferred study under PREA to evaluate the pharmacokinetics, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 12 years to 17 years of age.
- a. Final Protocol Submission Date: October 2016
 - b. Study/Trial Completion Date: October 2018
 - c. CSR Submission Date: October 2020
- 5) (b) (4)
-
- 6) Deferred study under PREA to evaluate the long-term safety of dextansoprazole for the (b) (4) maintenance of healing of erosive esophagitis (EE) in pediatric patients 1 month through 11 months of age, who require chronic treatment with dextansoprazole due to underlying conditions that predispose to chronic GERD and EE.
- a. Final Protocol Submission Date: August 2022
 - b. Study/Trial Completion Date: August 2028
 - c. CSR Submission Date: February 2029
- 7) Deferred study under PREA to evaluate the long-term safety of dextansoprazole for the (b) (4) maintenance of healing of erosive esophagitis (EE) in pediatric patients 1 year through 17 years of age, who require chronic treatment with dextansoprazole due to underlying conditions that predispose to chronic GERD and EE.
- a. Final Protocol Submission Date: August 2022
 - b. Study/Trial Completion Date: August 2028
 - c. CSR Submission Date: February 2029

Of note, in addition to the PREA requirements, Dexilant delayed-release capsules (NDA 22287) also has another post-marketing requirement (PMR) that was issued for adults based on findings of spontaneous post-marketing reports of potential for increased bone fractures with prolonged or high doses of proton pump inhibitors. The final clinical study report has been submitted and is currently under review by the Division at the time of this document.

Recommended Comments to Applicant

(b) (4)

In addition, the final labeling agreements and the recommendations regarding required post-marketing studies under PREA will also be included in the Approval Letter. A preliminary comment to the applicant is provided below. The final language for the Approval Letter is under review at the time of this document. For final recommendations that were communicated to the applicant, refer to the Approval Letter.

(b) (4)

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/s/

JULI A TOMAINO
01/25/2016