# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208056Orig1s000

# SUMMARY REVIEW

Deputy Division Director Review
Dexilant SoluTab (dexlansoprazole delayed-release orally disintegrating tablet)
Andrew E. Mulberg, MD, FAAP
January 25, 2016

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | |
| **From** | Andrew E. Mulberg, MD, FAAP, CPI |
| **Subject** | Division Deputy Director Summary Review |
| **NDA/BLA # Supplement #** | NDA 208056 |
| **Applicant Name** | Takeda Pharmaceuticals, USA, Inc. |
| **Date of Submission** | March 26, 2015 |
| **PDUFA Goal Date** | January 26, 2016 |
| **Proprietary Name / Established (USAN) Name** | Dexilant SoluTab (dexlansoprazole delayed-release orally disintegrating tablet) |
| **Dosage Forms / Strength** | 30 mg oral |
| **Proposed Indication(s)** | (b) (4)<br>2. Maintaining healing of EE and relief of heartburn,<br>3. Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease GERD |
| **Action/Recommended Action for NME:** | Approval of Dexilant SoluTab 30 mg for the following indications:<br>- Maintaining healing of erosive esophagitis and relief of heartburn.<br>- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.<br>(b) (4) |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | Juli Tomaino, MD |
| CDTL Review | Juli Tomaino, MD |
| OPQ Review Drug Substance (OPQ/ONDP/DNDAPI/ Branch II) | B. Stevens, PhD, MPH, D. Christner, PhD |
| OPQ Review Drug Product and Environmental Assessment | H. Shafiei, PhD, M. Rhee, PhD |

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|---|---|
| (ONDP/DNDP II/ Branch IV) | |
| Application Technical Lead (ONDP/DNDP II/ Branch IV) | H. Shafiei, PhD |
| Labeling review (OPDP, DMPP) | M. Patel, PharmD, K. Dowdy, RN, BSN |
| OPQ Biopharmaceutics (OPQ/DB/Branch II) | P. Duan, PhD, T. Chen, PhD |
| OPQ Microbiology and Process Review (OPF/Division of Process Assessment II/Branch V) | Y. Tang, PhD; C. Cruz, PhD |
| OPQ Review Facility (OPF/DIA/Branch III) | M. Heayn, J. Williams, Grace E McNally,X. Shen |
| OSI (Bioequivalence Establishment Inspection) | M. Heayn/S. Nkah |
| Clinical Pharmacology Reviewer | Dilara Jappar, Ph.D. |
| Labeling review (OSE/DMEPA) | S. Abraham, RPh, K. Worthy, PharmD, L. Merchant, PharmD, |

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

# Signatory Authority Review Template

## 1. Introduction

Takeda currently markets dexlansoprazole (Dexilant®) for the following indications:

1) Healing of all grades of Erosive Esophagitis (EE)
2) Maintaining of healing EE
3) Treating heartburn associated with symptomatic non-erosive Gastroesophageal Reflux Disease (GERD).

In this NDA supplement, 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 [OD] tablets). 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.

## 2. Background

Dexlansoprazole (formerly approved under the name of Kapidex) received NDA approval (N22-287), January 30th, 2009 for the following adult indications:

**Table 1: Approved Dexilant Indications**

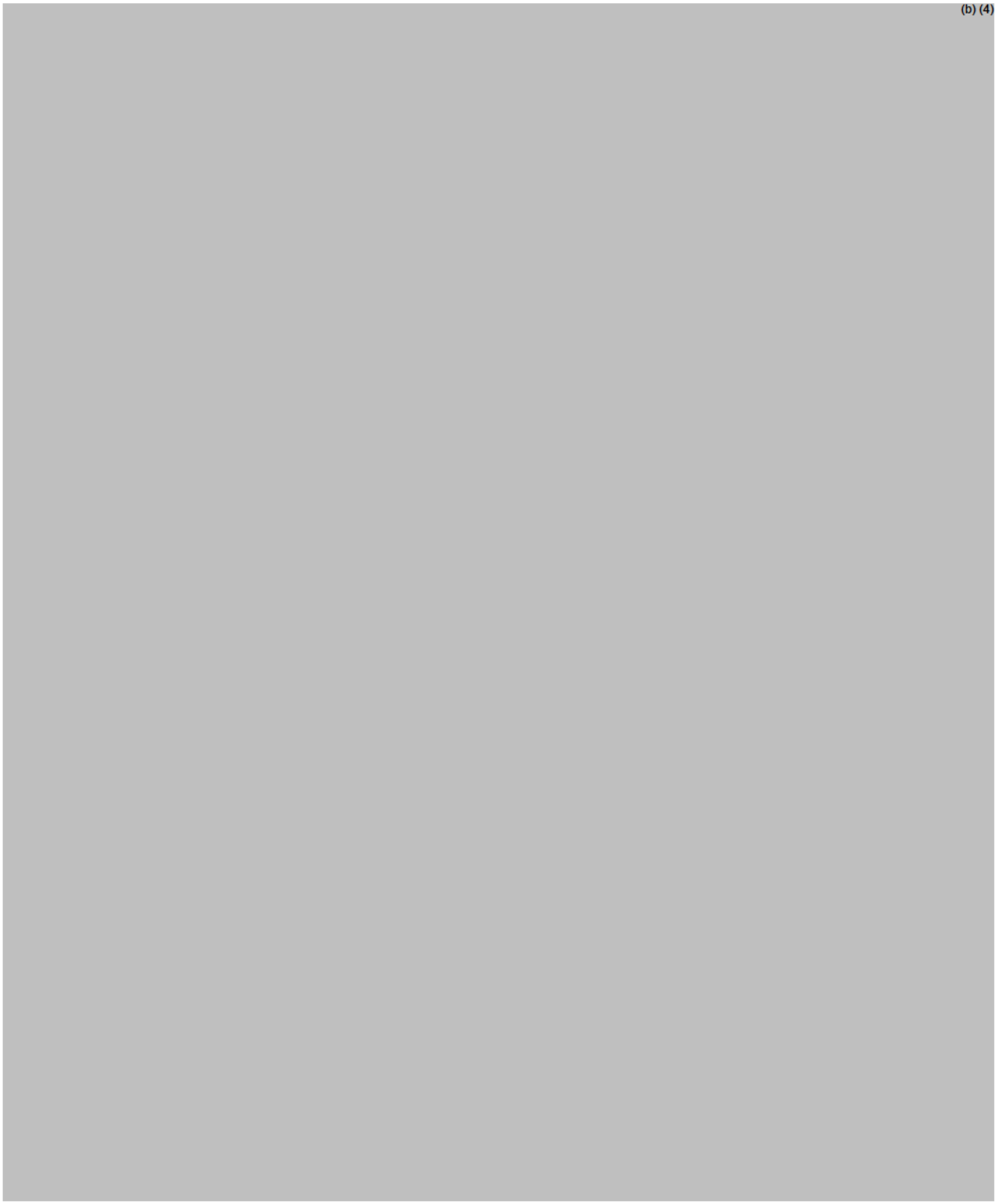
| Indication | Dose | Frequency |
|---|---|---|
| Healing of all grades of EE | 60 mg | Once daily for up to 8 weeks |
| Maintaining of healing EE | 30 mg | Once daily* |
| Treating heartburn associated with symptomatic non-erosive GERD | 30 mg | Once daily for 4 weeks |

*Controlled studies did not extend beyond 6 months.

Gastroesophageal reflux disease is a common gastrointestinal disorder characterized as symptomatic and erosive types, the latter which requires maintenance of healing, which can be accomplished by the use of multiple different proton pump inhibitors (PPIs). Dexilant (dexlansoprazole) is the *R*-enantiomer of the racemate lansoprazole. The *R*-enantiomer has demonstrated a prolonged pharmacokinetic and pharmacodynamic profile compared to that of the *S*-enantiomer because the *S*-enantiomer is rapidly cleared from circulation. Dexlansoprazole is formulated as a delayed release capsule consisting of two granules, a fast-release granule (within first hour) and a slow-release granule (within 4-5 hours), designed to provide extended pharmacological activity. Dexlansoprazole acts by blocking the ($H^+$, $K^+$)-ATPase proton pumps of parietal cells of the stomach. This action suppresses acid secretion,

raises the pH of the stomach, and decreases damage to the esophageal mucosa during episodes of acid reflux.

(b) (4)



(b) (4)

The supplementary trial results submitted for this application were submitted to address additional labeling revisions and were proposed to update Section 14 Clinical Studies of the current product labeling.

## 3. CMC

In the CDTL memorandum, Dr. Tomaino notes that 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. The reader is referred to the OPQ Integrated Quality Assessment review, dated 12/24/2015, for the full complete information.

## 4. Nonclinical Pharmacology/Toxicology

The reader is referred to the summary of Dr. Tomaino in the CDTL memorandum for details. Drs. Zhang and Joseph have not recommended PMCs or PMRs. The final labeling includes recommended changes by the nonclinical reviewer and DPMH consultant. One interesting point relates to the use of the excipient, (b) (4) methacrylate co-polymer, (b) (4) which has been used at lower amounts in two approved drug products. The nonclinical reviewers have noted that (b) (4) contained in Dexilant SoluTab does not raise safety concerns for use in adults. As stated in the nonclinical review, the overall toxicity data can also support higher doses (mg/kg) of (b) (4) which may be potentially needed for future pediatric labeling.

## 5. Clinical Pharmacology

For a detailed review of the clinical pharmacology data provided in this NDA, refer to the clinical pharmacology review by Dr. D. Jappar (primary review), and Drs. S. Lee and Dr. H. Ahn (secondary reviewers), dated 12/23/2015. 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.

The data supporting this conclusion are reflected below in **Table 2** which demonstrate the bioequivalence of the Dexilant SoluTab versus the Dexilant Delayed release 30 mg capsule at Days 1 and 5. Data all fall 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 intra-gastric pH profile was similar between dexlansoprazole ODT 30 mg and Dexilant delayed-release capsule 30 mg.

**Table 2: 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**

| 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** | | | |
| Cmax | 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** | | | |
| Cmax | 108.57 | 95.53 | 123.39 |
| AUC(0-tlqc) | 94.90 | 86.57 | 104.04 |
| AUC(0-tau) | 94.65 | 86.36 | 103.73 |

(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. Data from Study TAK-390MR(OD)-104, 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. Two dexlansoprazole ODT 30 mg tablets were not bioequivalent (BE) to one Dexilant 60 mg capsule. These data are reflected below in **Table 3** which demonstrate that the AUC is far below the 0.8-1.25 BE range.

**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**

| 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)** | | | |
| Cmax | 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)** | | | |
| Cmax | 93.61 | 84.93 | 103.18 |
| AUC(0-tlqc) | 77.88 | 70.71 | 81.1 |
| AUC(0-tau) | 78.23 | 72.55 | 84.37 |

(b) (4)

The clinical pharmacology reviewers explored the potential implication of the differences in AUC on efficacy and safety. Intra-gastric 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 reader is referred to the CDTL memorandum and reviews by Clinical Pharmacology for description of alcohol dose dumping, food and water effects studies that support the current recommendations for Section 2.3 of the label.

The Signatory agrees with the recommendations of the Clinical Pharmacology reviewers.

## 6. Clinical Microbiology

Clinical microbiology considerations do not apply to this supplemental application because the product is not an antimicrobial product.

## 7. Clinical/Statistical-Efficacy

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

## 8. Safety

The safety data from the 6 phase 1 studies were pooled into an integrated safety database by the applicant**. Table** below summarizes the **2:** Summary of Studies included in Pooled Safety Analyses:

**Table 2: 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) |

**Adapted from Dr. Tomaino, CDTL memorandum**

Dr. Tomaino summarized the disposition, demographics, and adverse events by treatment received, dexlansoprazole capsules, dexlansoprazole ODT, or dexlansoprazole capsules and ODT combined. The subjects were administered the following doses depending on the trial, as described above in: dexlansoprazole ODT 30 mg, dexlansoprazole ODT 30 mg x 2, dexlansoprazole capsules 30 mg, and dexlansoprazole capsules 60 mg. I concur with Dr. Tomaino's medical review of the safety information including postmarketing safety information conducted for this supplement confirming no new adverse reactions associated with treatment with Dexilant ODT with the exception of headache, Dr. Tomaino concluded that in general, the adverse events reported during the pooled phase 1 studies are consistent with the known safety profile of Dexilant delayed-release capsules. A review of the safety information submitted in this application does not provide any new or significant safety information.

## 9. Advisory Committee Meeting

During this review cycle, an advisory committee meeting was not convened to discuss the current supplement

## 10. Pediatrics

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) to maintain healing of EE (b) (4) and waiver request 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. The changes to the pediatric program since the Agreed iPSP, dated December 11, 2014 reflect (b) (4) under this Dexilant SoluTab NDA 208056. 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. The timelines for this revised timelines is reflected in the PREA-required study dates listed below in Section 13.2

## 11. Other Relevant Regulatory Issues

**A. DSI audits**

None performed during this sNDA review.

**B. 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).

# 12. Labeling

## 1. Waiver of Highlights Section:

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling. Justification for this decision is based on the fact that the review team made efforts to reduce the length of Highlights, as recommended in the Labeling Review Tool, but that due to the fact that the prescribing information contains information on two dosage forms with different indications and dosage and administration instructions, the relevant information could not be reduced to meet the 1/2 page requirement. The Sponsor's request for a waiver should be granted.

## 2. 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.

## 3. 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 Dexilant® SoluTab 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 SoluTab.

### *4. 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. For final labeling agreements, the reader is referred to the approved product label.

# 13. Decision/Action/Risk Benefit Assessment

**13.1 Regulatory Action**:
The Clinical and Clinical Pharmacology reviewers recommended approval (b) (4) which is further discussed below.

**13.2 Risk Benefit Assessment:**
Dexilant ODT is a new formulation of delayed release dexlansoprazole which offers potential for increased compliance based on its mode of administration to adults. The pediatric implications of this new drug formulation will be addressed as PREA requirement studies which are outlined below. Dexilant® SoluTab has proven its positive risk benefit calculus, is bioequivalent as a formulation to the Dexilant capsules and therefore based on equivalent safety of the Dexilant® SoluTab, I concur with the Approval recommendation for the indications (b) (4)
(b) (4)

The data provided in the NDA submission failed to demonstrate bioequivalence between two Dexilant SoluTab 30 mg tablets and one Dexilant delayed-release capsule 60 mg (b) (4)

(b) (4)

(b) (4)

**Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:**
There are no requirements for postmarketing risk evaluation and mitigation strategies.

**Recommendation for other Postmarketing Requirements and Commitments**
Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

3091-2 Deferred study under PREA to evaluate the pharmacokinetics of dexlansoprazole, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 1 year to 11 years of age.

| | |
|---|---|
| Final Protocol Submission: | 10/2020 |
| Study Completion: | 10/2024 |
| Final Report Submission: | 10/2025 |

3091-3 Deferred study under PREA to evaluate the pharmacokinetics of dexlansoprazole, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 12 years to 17 years of age.

| | |
|---|---|
| Final Protocol Submission: | 10/2016 |
| Study Completion: | 10/2018 |
| Final Report Submission: | 10/2019 |

3091-4 Deferred pediatric study under PREA for treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD) in pediatric patients aged 1 year to 11 years.

| | |
|---|---|
| Final Protocol Submission: | 10/2020 |
| Study Completion: | 10/2024 |
| Final Report Submission: | 10/2025 |

3091-5 Deferred pediatric study under PREA for treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD) in pediatric patients aged 12 year to 17 years.

| | |
|---|---|
| Final Protocol Submission: | 10/2016 |
| Study Completion: | 10/2018 |

Final Report Submission: 10/2019

3091-6 Deferred study under PREA to evaluate the long-term safety of dexlansoprazole for the maintenance of healing of erosive esophagitis (EE) in pediatric patients 1 month through 11 months of age, who require chronic treatment with dexlansoprazole due to underlying conditions that predispose to chronic gastroesophageal reflux disease (GERD) and relapsing EE.

| | |
|---|---|
| Final Protocol Submission: | 08/2022 |
| Study Completion: | 08/2028 |
| Final Report Submission: | 02/2029 |

3091-7 Deferred study under PREA to evaluate the long-term safety of dexlansoprazole for the maintenance of healing of erosive esophagitis (EE) in pediatric patients 1 year through 17 years of age, who require chronic treatment with dexlansoprazole due to underlying conditions that predispose to chronic gastroesophageal reflux disease (GERD) and relapsing EE.

| | |
|---|---|
| Final Protocol Submission: | 08/2022 |
| Study Completion: | 08/2028 |
| Final Report Submission: | 02/2029 |

Of note, in addition to the PREA requirements for Dexilant® delayed-release capsules (NDA 22287) another post-marketing requirement (PMR) 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.

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/s/

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ANDREW E MULBERG
01/25/2016