

## Cross-Discipline Team Leader Review

<b>Date</b>	July 1, 2016
<b>From</b>	Juli Tomaino MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 22287/1226
<b>Supplement#</b>	
<b>Applicant</b>	Takeda Pharmaceuticals, USA, Inc.
<b>Date of Submission</b>	September 30, 2015
<b>PDUFA Goal Date</b>	July 29, 2016
<b>Proprietary Name / Established (USAN) names</b>	Dexilant (dexlansoprazole delayed-release capsule)
<b>Dosage forms / Strength</b>	60 mg and 30 mg oral
<b>Proposed Indication(s)</b>	<ol style="list-style-type: none"> <li>1. Healing of all grades of erosive esophagitis (EE)</li> <li>2. Maintenance of healed EE and relief of heartburn</li> <li>3. Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD)</li> </ol>
<b>Recommended:</b>	<p>Approval of expanding the following indications to include <u>pediatric patients 12 years of age and older</u>:</p> <ol style="list-style-type: none"> <li>1. Healing of all grades of erosive esophagitis (EE)</li> <li>2. Maintenance of healed EE and relief of heartburn</li> <li>3. Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD)</li> </ol>

## 1. Introduction

On September 30, 2015, Takeda Pharmaceuticals, USA, Inc. (the applicant) submitted a supplemental new drug application (sNDA) to support marketing approval of expanding the indications for Dexilant (dexlansoprazole delayed-release capsules) to include pediatric patients 12 years of age and older. Dexlansoprazole is currently available in two dose strengths and two formulations as:

- 1) Dexilant delayed-release capsules, 30 mg and 60 mg, approved on January 30, 2009 (NDA 22287)
- 2) Dexilant SoluTab (dexlansoprazole delayed-release orally disintegrating tablets), 30 mg, approved on January 26, 2016 (NDA 208056).

The currently labeled indications and dosage for Dexilant (dexlansoprazole delayed-release capsules) include the following:

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

The currently labeled indications and dosage for Dexilant SoluTab include the following:

- Maintenance of healed EE and relief of heartburn: 30 mg once daily for up to 6 months.
- Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD): 30 mg once daily for 4 weeks.

In support of this supplemental NDA, the applicant conducted two clinical trials in pediatric patients 12 to 17 years of age, including one trial to evaluate the safety and effectiveness of dexlansoprazole delayed-release capsules for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux (sGERD), and a second trial for the healing of erosive esophagitis (EE), and maintenance of healed EE and relief of heartburn. The applicant also included the results of a phase 1, pharmacokinetic (PK) and safety trial in patients 12 to 17 years of age since PK was not assessed during the two clinical safety and efficacy trials.

The review of this application was conducted as a Standard review with a Prescription Drug User Fee Act (PDUFA) goal date of July 29, 2016. All of the review disciplines recommend in favor of approval for the indications of healing of EE, maintenance of healed EE and relief of heartburn, and treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) in patients 12 years of age and older.

This memo summarizes the information contained in sNDA 22287/1226 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.<sup>1</sup> 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 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.<sup>2</sup> Management of GERD involves acid suppression therapy (e.g., H<sub>2</sub>-receptor antagonists or proton pump inhibitors) and lifestyle modification. For severe, refractory cases, surgical intervention may be an option.

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

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

Dexlansoprazole is a proton pump inhibitor (PPI) that inhibits the H<sup>+</sup>/K<sup>+</sup>/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. Dexilant (dexlansoprazole delayed-release capsules) was approved on January 30, 2009 for use in adults for healing of all grades of EE, maintenance of healed EE, and treatment of heartburn associated with symptomatic non-erosive GERD. The indication for maintenance of healed EE was expanded to include the relief of heartburn in 2011, upon approval of a supplemental NDA. An overview of the regulatory history is described below.

### Regulatory Background

Key components from the regulatory history are summarized below; refer to the clinical review by Dr. T. Altepeter, dated 6/23/2016, for further details.

January 30, 2009: Dexilant (dexlansoprazole delayed-release capsule), 30 mg and 60 mg, was approved for adults for the indications of healing of all grades of erosive esophagitis (EE), maintenance of healed EE, and treatment of 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 treatment of heartburn associated with sGERD is 30 mg once daily for up to 6 months and 4 months, respectively.

The following postmarketing Pediatric Research Equity Act (PREA) requirements were issued. This document will review the PREA PMRs related to studies in pediatric patients 12 to 17 years of age and are show in **bold type below**.

- 1356-1: Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 1 year to 11 years (modified 6/17/2011, see below).
- **1356-2: Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 12 years to 17 years (modified 6/17/2011, see below).**
- 1356-3: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 month to 11 months (waived 6/17/2011).
- 1356-4: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 year to 11 years.
- **1356-5: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years.**

November 2, 2009: A Type C meeting was held to discuss changes to the proposed clinical trials in patients 12-17 years of age with erosive esophagitis and symptomatic GERD. Agreements were made on the proposed sample size, overall study design, and doses to evaluate the safety and effectiveness of dexlansoprazole in pediatric patients 12 -17 years of age. Refer to the final meeting minutes, dated 12/9/2009 for full details.

June 17, 2011: An efficacy supplement for Dexilant (dexlansoprazole delayed-release capsule) (NDA 22287) was approved that expanded the indication for maintenance of healed

EE to also include the relief of heartburn. Modifications to the PREA deferred studies allowed for better assessment of the need to maintain healing of EE in pediatric patients. PREA deferred studies #1356-1 and #1356-2 were modified, while #1356-3 was waived. Additional PREA studies were added to be conducted in pediatric patients with predisposing factors for chronic gastroesophageal reflux disease and erosive esophagitis. The revised and new PREA required studies are listed below. It should be noted that there were no modifications to PREA Study1356-5 at the time of efficacy supplement approval.

- **1788-1 (formerly 1356-2): Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 12 years to 17 years of age.**
- 1788-2: Deferred study under PREA to evaluate the pharmacokinetic, pharmacodynamic, and safety profiles of dexlansoprazole in patients 1 month to 11 months of age with endoscopy-proven erosive esophagitis (EE).
- 1788-3 (formerly 1356-1): Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 1 year to 11 years of age.
- 1788-4: Deferred study under PREA to evaluate the long-term safety of dexlansoprazole for the healing and 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 and relapsing EE.
- 1788-5: Deferred study under PREA to evaluate the long-term safety of dexlansoprazole for the healing and 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 and relapsing EE.

December 14, 2011: A Type C meeting was held to discuss the amended protocols addressing PMRs for 12 to 17 year old patients. During that meeting, the Division generally agreed with the proposed study plan. The key discussion items and recommendations are below:

- The Division recommended that the study duration to assess healing of EE should be 8 weeks, to align with adult trials. The applicant agreed, and clarified that patients who are not healed at 8 weeks would be discontinued and would receive standard of care treatment.
- The applicant provided information to support that the electronic patient diary had been revised to ensure age-appropriateness.
- The Division proposed that patients should be followed for at least 3 months after completing the treatment phase of study 207.
- The Division expressed agreement with planned doses.
- The applicant agreed to collect sample for genotyping of all patients for CYP2C19 to explore correlation with safety and efficacy.
- The applicant agreed to include 24 hour urine collection for urinary magnesium excretion for any patient that develops hypomagnesemia during the trial.

March 5, 2012: Final protocols were submitted for the following trials intended to fulfill the PREA PMRs in pediatric patients 12 to 17 years of age.

- Study TK-390MR\_206 “A phase 2, open label, multicenter, 4 week study to assess the safety and effectiveness of daily oral administration of dexlansoprazole delayed-release capsules for relief of heartburn, in adolescent patients aged 12 to 17 years with symptomatic non-erosive gastroesophageal reflux disease” was submitted to address PREA PMR 1356-5.
- Study TK-390MR\_207 “A Phase 2, multicenter, 36 week study to assess the safety and effectiveness of daily oral administration of dexlansoprazole delayed-release capsules for the healing of erosive esophagitis and maintenance of healed erosive esophagitis and relief of heartburn, in adolescent patients aged 12 to 17 years” was submitted to address PREA PMR 1788-1

December 11, 2014: The applicant was notified of agreement to the iPSP (Pediatric Study Plan) for Dexilant SoluTab (NDA 208056), submitted November 19, 2014. Of note, Dexilant delayed-release capsules (NDA 22287) pre-dated the requirement for an iPSP.

January 26, 2016: Dexilant SoluTab (dexlansoprazole delayed-release orally disintegrating tablet), 30 mg, was approved for adults for the indications of maintenance of healed EE, and treatment of heartburn associated with symptomatic non-erosive GERD (sGERD).

September 30, 2015: The supplemental new drug application (sNDA) 22287/1226 (the application reviewed in this document) was submitted to support approval of expanding the current Dexilant indications to include pediatric patients 12 years of age and older, and fulfillment of PREA PMR 1788-1 and 1356-5. The pediatric trials conducted to support labeling in pediatric patients 12 to 17 years of age utilized Dexilant delayed-release capsules. This document will focus on the pediatric trials that were conducted using the Dexilant capsules; however, the labeling for patients 12 years and older will apply to both the Dexilant capsules and Dexilant SoluTab. Dexilant SoluTab 30 mg was approved based on the establishment of bioequivalence to the Dexilant 30 mg capsule. As part of the Dexilant SoluTab iPSP, the Division communicated that the planned/ongoing safety and efficacy trials of dexlansoprazole capsules in pediatric patients may, upon review, fulfill the pediatric assessment for Dexilant SoluTab. The iPSP for Dexilant SoluTab was presented to PeRC on December 9, 2015. The pediatric assessment for sNDA 22287/1226 was presented to PeRC on May 26, 2016 and PeRC agreed with the Division’s approach and recommendation for approval.

Therefore, the clinical trials submitted in this submission will fulfill the PREA PMRs for the pediatric indications in the 12 to 17 year age group for both Dexilant capsule (NDA 22287) and Dexilant SoluTab (NDA 208056). The PREA PMRs that will be fulfilled upon approval of this efficacy supplement are below.

- NDA 22287
  - 1356-5: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years.

- 1788-1: Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 12 years to 17 years of age.
- NDA 208056
  - 3019-4: 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.
  - 3019-2: 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.

Submission and Review

The supplemental NDA was received electronically on September 30, 2015, and granted a Standard Review status with a PDUFA goal date of July 29, 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	T. Altepeter, MD, dated 6/23/2016
Statistical Review (DBIII)	A. Parfionovas, PhD, Y. Chen, PhD, dated 6/24/2016
Nonclinical (DGIEP)	K. Zhang, PhD, D. Joseph, PhD (NAI)
OPQ Review and Environmental Assessment (DNDP II/ONDP/Branch V)	D. Gromek-Woods, PhD, Moo-Jhong Rhee, PhD, dated 6/22/2016
Clinical Pharmacology Review (OCP/DCP3)	S. Li, PhD, S. Lee, PhD., dated 6/13/2016
Labeling review (OPDP, DMPP)	M. Patel, PharmD, dated 5/18/2016, and L. Griffiths, MSHS-PH, BSN, RN, M. Williams, PhD, K. Dowdy, RN, BSN, dated 5/17/2016
OSI (Clinical Site Inspection)	S. Leibenhaut, MD/S. Thompson/K. Ayalew, dated 4/7/2016
Labeling review (OSE/DMEPA)	S. Abraham, RPh, M. Mistry, PharmD, dated 5/27/2016
Other: Consultation review (DPMH)	Maternal health review: M. Dinatale, MD/T. Johnson, MD/L. Yao, MD, dated 6/2/2016. Pediatric review: A. Taylor, MD/H. Sachs, MD/J. Alexander, dated 6/13/2016

DGIEP: Division of Gastroenterology and Inborn Errors Products, NAI: No Action Indicated, 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

There was no new CMC information submitted with this efficacy supplement. The OPQ reviewers recommend approval of this supplemental NDA. The reader is referred to the memo by Dr. D. Gromek-Woods, dated 6/22/2016, for the complete information.

### **CMC/Environmental Assessment**

The application requested a categorical exclusion from the preparation of an environmental assessment as stated in 21 CFR 25.31(b). The applicant's request for the categorical exclusion from the environmental assessment was granted.

### **3) Nonclinical Pharmacology/Toxicology**

No new nonclinical data were submitted with this efficacy supplement. No changes to the label and no PMR/PMCs were recommended.

### **4) Clinical Pharmacology/Biopharmaceutics**

The clinical pharmacology reviewers concluded that the supplemental NDA is acceptable for approval, provided an agreement on labeling is reached. In addition, the reviewers concluded that the applicant has fulfilled the PREA requirements for pharmacokinetics evaluation in patients 12-17 years of age, which is included in PMR 1788-1. The clinical pharmacology reviewers have not recommended PMCs or PMRs. The final labeling includes recommended changes by the clinical pharmacology reviewers. I agree with the recommendations made by the clinical pharmacology reviewers.

I have summarized the key findings from the clinical pharmacology review below. For a detailed review of the clinical pharmacology data provided in this sNDA, refer to the clinical pharmacology review by Dr. S. Li (primary review), and Dr. S. Lee (secondary reviewer), dated 6/13/2016.

The clinical pharmacology review evaluated the data submitted from study T-P107-163 entitled, "a Phase 1, Randomized, Open-Label, Parallel Group, Multicenter Study to Evaluate the Pharmacokinetics and Safety of Dexlansoprazole Modified Release Capsules (30 mg and 60 mg) in Adolescents with Symptomatic Gastroesophageal Reflux Disease." This PK and safety trial enrolled 36 pediatric patients 12 to 17 years of age who were administered dexlansoprazole delayed-release capsules 30 mg (18 patients) or 60 mg (18 patients) once daily for 7 days. All 36 patients completed the trial after receiving all 7 doses. The clinical pharmacology reviewer determined that the bioanalytical method used to determine dexlansoprazole concentrations was acceptable. The PK concentration-time profiles were similar to those observed in the adult trials; dexlansoprazole displayed 2 distinct peaks, reflective of the release characteristics of the two types of enteric-coated granules with different pH-dependent dissolution profiles that are present in dexlansoprazole capsules. The systemic exposure of dexlansoprazole increased approximately dose proportionally from 30 mg to 60 mg in pediatric patients 12 to 17 years of age, similar to that observed in adult patients. A summary of the plasma PK parameters of dexlansoprazole in pediatric patients 12 to 17 years of age is show below in Table 1.

Table 1: Summary of Plasma Pharmacokinetic Parameters of Dexlansoprazole in Pediatric Patients 12 to 17 year of Age

	T <sub>max</sub> (hr)	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /Dose (ng/mL/mg)	AUC(0-tau) (ng-hr/mL)	AUC(0-tau)/ Dose (ng-hr/mL/mg)	T <sub>1/2(a)</sub> (hr)	CL/F (L/hr)
<b>Regimen A: Multiple 30 mg Dose – Subjects Age 12-17 years – Day 7</b>							
N	17	17	17	16	16	16	16
Mean	4.65	691	23.0	2886	96.21	1.66 [1.32]	12.8
SD	2.909	367.5	12.25	1355.2	45.173	0.871	6.09
Min	1.00	255	8.50	1204	40.12	0.63	5.2
Median	5.00	609	20.30	2520	83.99	1.43	11.9
Max	12.00	1600	53.33	5741	191.36	3.74	24.9
%CV	63	53	53	47	47	52	48
<b>Regimen B: Multiple 60 mg Dose – Subjects Age 12-17 years – Day 7</b>							
N	18	18	18	18	18	18	18
Mean	3.31	1136	18.9	5120	85.3	2.59 [2.04]	15.3
SD	1.519	582.2	9.70	2986.5	49.77	1.379	7.52
Min	1.00	399	6.65	1996	33.27	0.95	4.9
Median	3.50	1045	17.42	4124	68.73	2.36	14.57
Max	6.03	2620	43.67	12246	204.10	6.30	30.05
%CV	46	51	51	58	58	53	49

(source: clinical pharmacology review by Dr. S. Li, page 4/23, dated 6/13/2016)

The clinical pharmacology reviewer evaluated the comparison of pharmacokinetics between adult and pediatric patients 12 to 17 year of age. The systemic exposures of dexlansoprazole in pediatric patients 12 to 17 years of age who received dexlansoprazole 30 mg or 60 mg were similar to healthy adults or adult patients with GERD.

*Adolescent patients vs. healthy adults:* Following oral administration of dexlansoprazole 30 mg daily, the mean (%CV) C<sub>max</sub> and AUC(0-tau) at steady state in pediatric patients 12-17 years of age were 691 (53%) ng/mL and 2886 (47%) ng.h/mL, respectively, and were 658 (40%) ng/mL and 3275 (47%) ng.h/mL, respectively in healthy adults. For the 60 mg daily dose, the mean C<sub>max</sub> and AUC(0-tau) at steady state in adolescent patients were 1136 (51%) ng/mL and 5120 (58%) ng.h/mL, respectively, and were 1397 (51%) ng/mL and 6529 (60%) ng.h/mL, respectively, in healthy adults. The mean PK parameters for healthy adults and pediatric patients are shown below in Table 2.

*Adolescent patients vs. adult patients:* In one study (Study T-P105-129) with adult patients mean systemic exposures for dexlansoprazole appeared higher than the mean values in adolescent patients. However, based on the review of individual PK data, the higher mean exposures in adult patients were due to two patients with particularly high exposures. The reason for the higher exposure in those two adult patients is unknown; however, the high exposures may be explained by use of concomitant medications that are CYP2C19 inhibitors resulting in higher systemic exposures. Overall, individual C<sub>max</sub> and AUC values in adolescent patients were similar to those observed in the rest of adult patients.

Table 2: Pharmacokinetic Parameters for Patients 12 to 17 years of age and Healthy Adult Subjects Following Multiple Daily 30 or 60 mg Oral Doses of Dexlansoprazole Capsules

	N	t <sub>max</sub> (hr)	C <sub>max</sub> (ng/mL)	AUC <sub>24</sub> or AUC <sub>τ</sub> (a) (ng·hr/mL)	t <sub>1/2z</sub> (hr)	CL/F (L/hr)
<b>Multiple 30 mg Dose – Adolescent GERD Subjects – Day 7 Data</b>						
Mean	17 (b)	4.65	691	2886	1.66	12.8
%CV		63	53	47	52	48
<b>Multiple 30 mg Dose – Healthy Adult Subjects – Day 5 Data</b>						
Mean	44 (c)	4.45	658	3275	1.75	11.4
%CV		37	40	47	49	48
<b>Multiple 60 mg Dose – Adolescent GERD Subjects – Day 7 Data</b>						
Mean	18	3.31	1136	5120	2.59	15.3
%CV		46	51	58	53	49
<b>Multiple 60 mg Dose – Healthy Adult Subjects – Day 5 Data</b>						
Mean	79 (d)	4.64	1397	6529	1.83	11.6
%CV		46	51	60	52	46

(a) AUC<sub>24</sub> for healthy adults and AUC<sub>tau</sub> for pediatric patients 12 to 17 years of age (tau was 24 hours in pediatric study).

(b) N=16 for AUC<sub>tau</sub>, t<sub>1/2z</sub>, and CL/F.

(c) N=43 for AUC<sub>24</sub>, t<sub>1/2z</sub>, and CL/F.

(d) N=73 for AUC<sub>24</sub> and t<sub>1/2z</sub>; N=41 for CL/F.

(source: clinical pharmacology review by Dr. S. Li, page 5/23, dated 6/13/2016)

The clinical pharmacology reviewer summarized the safety findings reported for this PK and safety trial. Of the 36 patients enrolled, 12 (33%) patients experienced a total of 21 treatment-emergent adverse events (TEAE) during the 7-day study: 39% patients who received dexlansoprazole 30 mg and 28% patients who received dexlansoprazole 60 mg. The most commonly reported TEAEs included reports of abdominal pain (4/36 [11%] patients), headache (3/36 [8%] patients), vomiting, dizziness, and presyncope (2/36 [6%] patients each), and similar to the adverse events reported in the larger, safety and efficacy trials reviewed under this efficacy supplement. While the sample size was small for each treatment group, the clinical pharmacology reviewer did not identify an exposure-response relationship for the TEAEs reported in this trial. Safety was reviewed in further detail by the clinical reviewer and summarized below in Section 7 of this document.

For a detailed review of the clinical pharmacology data provided in this sNDA, refer to the clinical pharmacology review by Dr. S. Li (primary review), and Dr. S. Lee (secondary reviewer), dated 6/13/2016.

## 5) Clinical Microbiology

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

## 6) Clinical/Statistical- Efficacy

The reader is referred to the clinical review, by Dr. T. Altepeter, dated June 23, 2016, for a comprehensive review of the efficacy data. Also refer to the statistical review by Dr. A. Parfionovas (primary reviewer), Dr. Y. Chen (secondary reviewer). The applicant proposes to expand the current indications of healing of all grades of erosive esophagitis (EE), maintenance of healed EE and relief of heartburn, and treatment of heartburn associated with in symptomatic non-erosive GERD to include pediatric patients 12 to 17 years of age. Dr. Altepeter recommends approval of this supplemental NDA from a clinical perspective. I concur with her recommendations. Below I will summarize the key findings from her review.

The results from two clinical safety and efficacy trials conducted in pediatric patients 12 to 17 years of age were submitted in this supplemental NDA:

- Study TAK-390MR\_206 was a phase 2, open-label, multicenter, 4-week trial to evaluate the safety and effectiveness of once-daily oral administration of dexlansoprazole delayed-release 30 mg capsules in pediatric patients 12 to 17 years of age with symptomatic non-erosive GERD (referred to as study 206 in this document).
- Study TAK-390MR\_207 was a phase 2, multicenter, 36-week trial in pediatric patients 12 to 17 years of age to evaluate the safety and effectiveness of oral daily administration of (1) dexlansoprazole delayed-release 60 mg capsules in patients with EE for the healing of EE (8 weeks), and (2) dexlansoprazole delayed-release 30 mg capsules or placebo in patients with healed EE for the maintenance of healed EE (16 weeks) and relief of heartburn. Patients who maintained healing during the double-blind placebo controlled 16-week phase to evaluate maintenance of healed EE were enrolled in an additional 12 week follow up period without therapy (referred to as study 207 in this document).

The statistical review team, Dr. A. Parfionovas and Dr. Y. Chen, confirmed the applicant's results and notes that although data from both efficacy trials supported the use of dexlansoprazole in pediatric patients 12 to 17 years of age for the proposed indications, the trials were not statistically powered. Therefore, only descriptive statistics, including the observed event rates and corresponding confidence intervals, should be described in the product label. The statistical reviewers state that the trial was conducted in accordance with the statistical analysis plan prospectively agreed upon by the Agency.

The efficacy results and rationale for extrapolation are summarized below.

### **Study 206: treatment of symptomatic non-erosive GERD**

#### *Study Design Overview*

The applicant conducted a single-arm, open-label, multi-center trial in 104 pediatric patients 12 to 17 years of age with symptomatic non-erosive GERD who were treated with dexlansoprazole 30 mg capsules once daily for 4 weeks to support the approval and product labeling of dexlansoprazole 30 mg for the treatment of symptomatic non-erosive GERD (sGERD) in pediatric patients  $\geq 12$  years of age. Patients with a documented history of GERD symptoms for at least three months prior to screening, reported heartburn on at least 3 out of 7 days during screening, and no esophageal erosions as confirmed by endoscopy were eligible

for enrollment into the trial. The primary outcome was safety, defined as treatment emergent adverse events (TEAEs) observed in  $\geq 5\%$  of patients. The secondary outcome (primary efficacy endpoint) was the percentage of 24 hour periods without daytime or nighttime heartburn. Reports of heartburn were collected directly from patients and recorded in a daily electronic diary (eDiary). The medical officer review notes that this efficacy endpoint was also utilized in the adult trials that supported product labeling for the indication of treatment of sGERD; therefore, the endpoint definition appears to be reasonable for this study to facilitate extrapolation of efficacy from adult to adolescent patients with sGERD. Multiple other additional endpoints were evaluated and are discussed in detail in the clinical review by Dr. T. Altepeter; however, the additional endpoints are considered to be exploratory.

### Demographics

One hundred-four patients 12 to 17 years of age were enrolled into study 206, and 102 patients completed the trial. The mean age of enrolled patients was  $15 \pm 1.5$  years, with females accounting for 70% of the patients. All enrolled patients were included in the full analysis dataset. Two patients discontinued the study early due to adverse events (GERD and dizziness) and are discussed in greater detail in the medical officer review by Dr. T. Altepeter. The clinical reviewer did not identify imbalances in the demographics and baseline characteristics that could have affected the outcomes of the efficacy analyses.

### Efficacy Results

At baseline, patients reported a median of 14% of days with neither daytime nor nighttime heartburn (i.e., heartburn-free days). During the 4-week treatment period, the median percentage of days with neither daytime nor nighttime heartburn improved to 47%. The clinical reviewer concluded that the observed increase in the heartburn-free days from baseline demonstrates a meaningful improvement in symptoms for the pediatric patients in this trial. This result is generally similar to the results from the adult trials that supported product labeling for the treatment of sGERD. In the adult trials, the median percentage of 24-hour heartburn-free periods during the 4-week treatment period was 55% in the dexlansoprazole 30 mg arm and 19% in the placebo arm.

As described in the clinical review by Dr. T. Altepeter, efficacy will be extrapolated from adequate and well-controlled trials conducted in adults to support the pediatric indication of treatment of sGERD. The rationale to support extrapolation of efficacy is based on sufficiently similar pathophysiology of sGERD between adults and pediatric patients 12 to 17 years of age, and the similarity of disease progression and response to intervention. Pharmacodynamic data (e.g., intragastric pH) were not collected during the pediatric trials in this age group (12 to 17 years of age), and the efficacy outcomes relied on the ability of patients 12 to 17 years of age to report heartburn similarly to adult patients. The Division previously determined that for this indication and age group, patient reported symptoms (i.e., heartburn), collected by age-appropriate questionnaires, can be used to compare efficacy with similar measures used in the adult trials. The dose selection in this pediatric trial is supported by PK similarity to adults and the efficacy results of the trials conducted in adults with sGERD. Dexlansoprazole 30 mg is the approved dose for adults for the treatment of sGERD; in the adult trials that supported labeling and approval, no additional clinical benefit was observed with doses higher than 30 mg for the treatment of sGERD. Therefore, the dose (i.e., dexlansoprazole 30 mg daily)

selected for this pediatric trial appears reasonable for the treatment of sGERD in patients 12 to 17 years of age. In addition, dexlansoprazole is the sixth in class for proton pump inhibitors (PPI), the mechanism of action is understood, and extensive data are available from multiple products in this class of drugs, approved for this indication, to support the use of PPI therapy for the treatment of symptomatic non-erosive GERD. For these reasons, the use of dexlansoprazole in this age group is supported by evidence from adequate and well-controlled trials of dexlansoprazole delayed-release capsules in adults, and by safety and pharmacokinetic studies performed in pediatric patients.

### **Study 207: healing of EE and maintenance of healed EE and relief of heartburn**

#### **Study Design Overview**

The applicant conducted one multi-center, 36-week trial of 62 pediatric patients 12 to 17 years of age with a documented history of GERD for at least three months and endoscopically-proven EE to support approval and product labeling for the healing of all grades of EE, maintenance of healing EE and relief of heartburn in pediatric patients  $\geq 12$  years of age. The 36-week trial included an initial 8-week open-label phase to evaluate dexlansoprazole 60 mg capsules daily for the healing of EE. Patients with healed EE at week 8, confirmed by endoscopy, entered into a randomized withdrawal, double-blind, placebo controlled 16-week phase to evaluate dexlansoprazole 30 mg capsules or placebo for the maintenance of healed EE and relief of heartburn. Patients were then eligible to enroll into an additional 12 week follow-on phase without therapy. The trial was designed to assess whether there is a need for long-term treatment to maintain healing of EE in pediatric patients 12 to 17 years of age. The primary and secondary endpoints are described below.

#### Primary Endpoint:

- Treatment-emergent adverse events (TEAEs) experienced by  $\geq 5\%$  of patients during the 8-week treatment period for healing of EE.
- TEAEs experienced by  $\geq 5\%$  of subjects during the 16-week double-blind treatment period for maintenance of healed EE.

#### Secondary Endpoints:

- The percentage of patients with healing of EE by Week 8 as assessed by endoscopy.
- The percentage of patients who maintain healing of EE from Week 8 to Week 24 among the subjects who were healed at Week 8 as assessed by endoscopy.
- The percentage of days with neither daytime nor nighttime heartburn over the first 8 weeks of treatment as assessed by electronic daily patient diary (eDiary).
- The percentage of days with neither daytime nor nighttime heartburn over Weeks 8 to 24 as assessed by eDiary among the subjects who were healed at Week 8.

Several other additional endpoints were evaluated and are discussed in detail in the clinical review by Dr. T. Altepeter; however, the additional endpoints were considered to be exploratory.

#### **Demographics**

Patients with a documented history of GERD for at least three months and endoscopically-proven erosive esophagitis (EE), based on presence and severity of EE, defined by the Los Angeles (LA) Classification for Esophagitis, were eligible for enrollment into the trial. Sixty-

three patients were initially enrolled and one patient did not initiate treatment; therefore, 62 patients were treated during this trial. The mean age was 15 years (range 12-17 years), and slightly more males (61%) were enrolled compared to females (39%). Overall, patients had more mild disease as 97% of patients at baseline had LA grades A and B esophagitis. At baseline, one patient each had grade C and D.

### *Efficacy Results and Discussion*

#### *Healing of EE*

Of the 62 patients enrolled, 58 patients completed the 8 week open-label phase. Four patients discontinued early and 7/58 (12%) patients did not have documentation of healed EE, by endoscopy. Fifty-one of fifty-eight (88%) patients achieved healing of EE over 8 weeks of treatment. In the adult trials that supported product labeling, 85% and 87% of adults from two adequate and well-controlled trials, respectively, achieved healing of EE at week 8. In her review, Dr. Altepeter notes that while the pediatric patient population had predominately grades A and B esophagitis at baseline, the adult patients also had a majority of patients with grades A and B esophagitis (71%) compared with grades C-D (29%). The clinical reviewer concluded that since pediatric patients generally have more mild disease compared to adult patients with EE, the difference in severity of disease, based on LA grade, between the pediatric and adult populations does not impact the ability to determine the efficacy of dexlansoprazole for the healing of EE at week 8.

As described in the clinical review, the rates of healing were calculated as the number of patients healed based on endoscopy, divided by the number of patients with week 8 endoscopy results. Therefore, patients who dropped out early and did not undergo week 8 evaluation are not included in this calculation. As noted in the medical officer review, the reasons for early discontinuation were not all well-defined, and some patients may have discontinued due to treatment failure. Dr. Altepeter conducted a more conservative analysis, based on intention-to-treat principles, which included all 62 enrolled patients. This type of analysis would provide a rate of healing of 51/62 (82%) patients with healed EE at week 8. This rate of healed EE number is similar to the rate of healing, as calculated based on the pre-specified statistical plan (88%). Therefore, the clinical reviewer determined that this difference does not change the overall conclusions drawn from the data. Also, refer to statistical review by Dr. A. Parfionovas (primary reviewer) and Dr. Y. Chen (secondary reviewer) for further detail.

#### *Maintenance of Healed EE*

After the initial eight weeks of treatment, 51 patients with healed EE, confirmed by endoscopy, were randomized to receive treatment with dexlansoprazole 30 mg capsules or placebo, once daily for an additional 16 weeks. Thirty-eight patients completed the 16 weeks of maintenance therapy, and 46 patients had endoscopy data available for the efficacy analysis. Of the 46 patients with post-baseline endoscopy data, 18/22 (82%) patients in the dexlansoprazole group and 14/24 (58%) patients in the placebo group remained healed, confirmed by endoscopy, over the 16 week treatment period. Dr. Altepeter notes that while this small trial was not powered to detect a statistically significant difference between treatment groups, the proportion of patients who maintained healing on treatment was numerically greater as compared with placebo. In the adult trials that supported labeling to

support an indication of maintenance of healing EE, adult patients were treated for 6 months, and 66% of patients maintained healing the treatment group vs 14% in the placebo group ( $p < 0.00001$ ).<sup>3</sup>

Since the placebo rate in the pediatric trial was larger than the placebo rate reported from the adult trials, the review team considered the possible reasons for the higher rate of placebo responders observed in the pediatric trials. Overall, the pediatric patients had less severe disease (97% Los Angeles Classification Grades A/B) as compared to the adult patients (71% Los Angeles Classification Grades A/B), which may contribute to the higher placebo rate observed during the maintenance phase in the pediatric patients. In fact, the healing rate and maintenance of healing rates were numerically greater in patients with Grade B esophagitis who were treated with Dexilant compared to placebo (9/11 [82%] vs 1/8 [13%]). There were an insufficient number of patients with Grades C-D to determine if there are differences in healing based on initial LA grade. There was one patient with Grade C esophagitis who healed at week 8, and was later randomized to placebo; however, this patient did not maintain healing to week 24. There was one patient with Grade D at baseline who did not heal at 8 weeks, but improved to Grade B after 8 weeks of therapy. The data suggest that there may be a subset of patients who require maintenance therapy, including patients with more severe disease.

Another possible reason for the higher placebo rate observed in the pediatric trial as compared to the adult trial may be related to the differences in treatment duration between the pediatric and adult trials. Dr. Altepeter notes in her review that in the adult trials that supported approval, the trial duration was 6 months for maintenance of healing, and the placebo rate declined over time. At each endoscopic assessment time point, the placebo rate observed in the adult trials was 43% at 1 month, 23% at 3 months, and 14% at 6 months.<sup>4</sup> While the placebo rate observed in the pediatric trial is greater than the placebo rate reported from the adult trials, the pediatric patients had overall more mild disease and the primary efficacy endpoint endoscopy was conducted at an earlier time point (i.e., 4 months in the pediatric trial vs 6 months in the adult trials). Dr. Altepeter concluded that these factors likely contributed to the higher placebo rate observed in the pediatric trial.

In the clinical review, Dr. Altepeter considered the method that was used to calculate the rate of maintained healing. The percentage of patients who maintained healing was based on the total number of patients who had endoscopy results at week 24 (i.e., “evaluable patients”). The applicant included patients who discontinued prematurely but who underwent an early termination endoscopy in this calculation. Eight of the patients who discontinued study drug prematurely underwent a final endoscopy at the time of early termination. The clinical reviewer determined that the endoscopies were performed within reasonable proximity (between day 120 and 168) to the week 24 efficacy analysis assessment to permit inclusion of the results in the efficacy analysis. Therefore, Dr. Altepeter considers this to be reasonable handling of the early termination data in this situation. Patients who did not consent to a final endoscopy were not included in the analysis.

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<sup>3</sup> Approved product labelling for Dexilant, updated 2/2/2016, available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/022287s020lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022287s020lbl.pdf)

<sup>4</sup> Clinical review for Dexilant, NDA 22287, by Dr. Keith Amand, dated 8/29/2008

The statistical and clinical reviewers each conducted a sensitivity analysis by treating the 5 patients who discontinued early and did not have endoscopy data as non-responders, shown below in Table 3. When the intent-to-treat (ITT) analysis was performed, the proportion of patients who maintained healing decreased slightly to 18/25 (72%) in the dexlansoprazole group and 14/26 (54%) in the placebo group. In addition, using a more conservative approach, when all patients who discontinued early are counted as failures, the proportion of patients who maintained healing decreases to 17/25 (68%) patients in the dexlansoprazole group and 12/26 (46%) in the placebo group. Using the most conservative approach, the rate of maintained healing is similar to the rate observed in the adult trials (66% maintained healing). Furthermore, the inclusion of a placebo group in the pediatric trial allows for a descriptive comparison to the dexlansoprazole group, where maintained healing of EE was numerically greater than placebo.

Table 3: Statistical Reviewer’s Analysis of Efficacy Endpoint for Maintenance of Healing at the End of the Double-Blind Phase

	<i>Original dataset</i>			<i>Early dropouts labeled as non-responders</i>		<b>Total</b>	
	<b>Maintained EE healing at the end of DB period</b>						
	<b>Yes</b>	<b>No</b>	<b>Total</b>	<b>Yes</b>	<b>No</b>		
<b>Dexilant 30 mg</b>	18 (82%)	4 (18%)	22	18 (72%)	7 (28%)	25	
<b>Placebo</b>	14 (58%)	10 (42%)	24	14 (54%)	12 (46%)	26	
<b>Total</b>	32	14		32	19	51	
<b>Responders % difference</b> (Dexilant - Placebo)	24%			18%			
Fisher’s exact test							
<b>p-value</b>	0.1141			0.2492			
<b>odds ratio</b>	3.21			2.20			
<b>95% CI</b>	(0.7, 16.7)			(0.6, 8.41)			

(source: table reproduced from statistical review, by Dr. A. Parfionovas and Dr. Y. Chen, dated 6/24/2016)

The statistical reviewer concluded that the applicant’s efficacy results for study 207 were confirmed to be numerically greater than placebo, but statistically non-significantly different from placebo. The trial was not adequately powered, and thus only descriptive statistics, including the observed event rates and the corresponding confidence intervals, should be included in the product labeling.

The reviewers concluded that the results of the ITT analyses do not change the overall conclusions and interpretation of the data; however, the reviewers recommended that the label should describe both the pre-specified completer analysis and the ITT analysis. Given that the completer analysis, as pre-specified, may introduce bias (i.e., by selecting for patients who underwent endoscopy), the review team determined that the ITT analysis, allowing patients who had an endoscopy at time they discontinued the trial to be imputed, should also be presented. I agree with the clinical and statistical recommendations; however, for future trials, I recommend using an ITT analysis with the completer analysis as supportive.

The statistical reviewer also performed the subgroup analysis for gender, age and region in the maintenance phase of the trial. In all subgroups, dexlansoprazole showed a higher rate of maintenance of healed EE than placebo. No inconsistency between subgroups was identified.

#### *Relief of Heartburn*

In addition to the maintenance of healed EE, the proposed indication also includes relief of heartburn. Reports of heartburn were collected directly from patients and recorded in a daily electronic diary (eDiary). Control of heartburn symptoms was assessed using the median percentage of heartburn free 24 hour periods. This measure is analogous to that used in the adult trials to support approval.

At baseline, the median percentage of days with neither daytime nor nighttime heartburn was 14% at baseline, increased to 66% over the initial 8-week healing phase, and further increased during the 16-week maintenance phase to 87% for patients receiving dexlansoprazole 30 mg as compared to 68% on placebo. While the placebo group reported a high rate of heartburn-free days, the patients were not largely symptomatic at the start of the maintenance phase, suggesting that the relief of heartburn symptoms is more closely associated with the initial healing of EE. However, the data support that symptoms remained well-controlled during the maintenance phase. While there was minimal change from baseline during the maintenance phase in the placebo group, the dexlansoprazole group experienced a numerically greater benefit for the relief of heartburn during the maintenance phase.

#### *Follow-on Phase (off therapy)*

At the conclusion of the maintenance treatment period (week 24), patients who maintained healing were followed, without continued treatment, for an additional 12 weeks, or until recurrence of symptoms that required intervention or treatment (e.g., endoscopy or re-initiation of acid suppression therapy). Follow-up was conducted at monthly clinic visit at weeks 28, 32, and 36. In addition, patients continued to complete daily eDiary to record symptoms.

Out of the 32 patients who maintained healing of EE at the end of the double-blind maintenance period, 27 patients (16 treated with dexlansoprazole and 11 treated with placebo in the double-blind phase) were followed for an additional 12-weeks without therapy. Twenty-four of the 27 patients completed the 12-week follow-up. One patient required treatment with acid suppression therapy, which suggests that therapy may be discontinued in most pediatric patients once EE is treated adequately.

#### *Conclusions*

Based on the reasons described previously in this document to support extrapolation of efficacy, including sufficiently similar pathophysiology of erosive esophagitis between adults and pediatric patients 12 to 17 years of age, and the similarity of disease progression and response to intervention, the clinical reviewer, Dr. Altepeter, concluded that the use of dexlansoprazole in pediatric patients 12 to 17 years of age is supported by evidence from adequate and well-controlled trials of dexlansoprazole capsules in adults, and by safety and pharmacokinetic studies performed in pediatric patients. I agree with the recommendations from the clinical and statistical reviewers.

## 7) Safety

The reader is referred to the clinical review, by Dr. T. Altepeter, dated June 23, 2016, for a comprehensive review of the efficacy data.

The clinical reviewer evaluated safety data collected from 104 patients enrolled in study 206 and 62 patients enrolled in study 207. Safety data from these two trials were evaluated separately, as the two trials differed in patient population, dosing, and duration of therapy. A combined analysis was also performed to assess the overall most common adverse events observed across the trials.

There were no deaths in either trial. There were no serious adverse events (SAE) in study 206. In study 207, 5 SAEs were reported. One SAE (substance abuse) occurred during the open-label phase, and the other 4 events occurred during the double-blind phase (2 in the dexlansoprazole group and 2 in the placebo group). No unique SAE was reported in more than one patient. The SAEs reported during the double-blind phase of study 207 included 1 event each of worsening of underlying erosive esophagitis and seizure-like episode in the 30 mg treatment group, and 1 event each of influenza infection and intentional overdose of illegal substances in the placebo group. Only one SAE (seizure like episodes) was considered possibly related to study drug.

Overall, treatment related adverse events (TEAE) were generally mild and self-limited. In study 206, 36/104 (35%) patients experienced at least one TEAE. The most commonly reported TEAEs seen in  $\geq 5\%$  of patients included abdominal pain, diarrhea, and headache. In study 207, TEAEs occurred with greater frequency, though it is important to note small sample size. In the open-label phase (dexlansoprazole 60 mg), 38/62 (61%) patients experienced at least one TEAE; the most commonly reported TEAEs seen in  $\geq 5\%$  of patients included headache, oropharyngeal pain, nasopharyngitis, abdominal pain, diarrhea, pharyngitis, and respiratory tract infection. In the double-blind phase (dexlansoprazole 30 mg vs placebo) the proportion of patients who experienced at least one TEAE was slightly higher in the treatment group (18/25 [72%]) compared with the placebo group (16/26 [62%]). The commonly reported TEAEs seen in  $\geq 5\%$  of patients and greater than placebo included headache, pharyngitis, sinusitis, insomnia, respiratory tract infection, and bronchitis. In the combined analysis for both study 206 and 207, the most common TEAEs in  $\geq 5\%$  patients included headache, abdominal pain, diarrhea, nasopharyngitis, and oropharyngeal pain.

Dr. Altepeter notes that abdominal pain and diarrhea were also among the most commonly reported AEs reported in the adult trials and are described in in the current labelling. In addition, she notes that abdominal pain is a common complaint of pediatric patients with GERD, and may represent ongoing symptoms of the underlying condition, rather than an adverse reaction due to the study drug. Her review also describes that headache was a commonly reported AE in the pediatric trials, but headache is not currently described in the label based on adult data. Therefore, Dr. Altepeter recommends that headache should be included in the product labelling. Overall, the AE profile was similar between adults and pediatric patients 12-17 years of age.

Additionally, patients were observed for adverse events of interest, known to be associated

with the proton pump inhibitor (PPI) drug class as described in the product labeling, including elevation of liver enzymes, hypomagnesemia, vitamin B12 deficiency, clostridium difficile colitis, and fractures.<sup>5</sup> Dr. Altepeter notes that the adverse events of interest were not identified in this submission, with the exception of a wrist fracture in one patient. The patient had no prior exposure to PPIs, was treated with dexlansoprazole for 52 days during the open label phase, and was later randomized to placebo. The fracture resolved with conservative treatment, and no bone density information was available. Dr. Altepeter determined that given the limited exposure to dexlansoprazole, and no history of prior exposure to PPIs, the fracture is unlikely related to treatment. Furthermore, it is difficult to make generalizable conclusions based on one patient.

The clinical reviewer did not identify any new safety signals. The laboratory data did not reveal any new safety signals or unexpected trends in clinical laboratory parameters.

In summary, Dr. Altepeter has concluded that adverse reactions to dexlansoprazole in pediatric patients 12 to 17 years of age appear to be consistent with prior experience with dexlansoprazole. I agree with Dr. Altepeter that no new safety concerns arose from the review of this efficacy supplement that would preclude approval.

## **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 reviews, by Dr. M. Dinatale, dated 6/2/2016, and Dr. A. Taylor, dated 6/13/2016, for further details. The DPMH recommendations have been incorporated into the final labeling.

### PREA Requirements

The pediatric assessment was presented to PeRC on May 25, 2016. PeRC agreed with the approach outlined by the Division.

The pediatric trials conducted to support labeling in pediatric patients 12 to 17 years of age utilized dexlansoprazole delayed-release capsules; however, the labeling for patients 12 years and older will apply to both the dexlansoprazole capsules (Dexilant) and dexlansoprazole orally disintegrating tablets (Dexilant SoluTab). Dexilant SoluTab 30 mg was approved based on the establishment of bioequivalence to the Dexilant 30 mg capsule. As part of the Dexilant SoluTab iPSP, the Division communicated that the planned/ongoing safety and efficacy trials of dexlansoprazole capsules in pediatric patients may, upon review, fulfill the pediatric assessment for Dexilant SoluTab. The iPSP for Dexilant SoluTab was presented to PeRC on

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<sup>5</sup> Approved product label for Dexilant, last revised 12/16/2015, available at Drugs@FDA, [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#abelinfo](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#abelinfo)

December 9, 2015. Upon approval, the pediatric assessments submitted in this supplemental NDA will fulfill the PREA PMRs for the pediatric indications in the 12 to 17 year age group for both Dexilant (NDA 22287) and Dexilant SoluTab (NDA 208056). The PREA PMRs that will be fulfilled upon approval of this efficacy supplement are below under the corresponding NDA.

NDA 22287

1356-5: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years.

1788-1: Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 12 years to 17 years of age.

NDA 208056

3019-4: 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.

3019-2: 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.

Proposed Pediatric Study Request (PPSR)

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

- 1) Healing of erosive esophagitis (EE) in pediatric patients 1 to 11 months of age and 12 to 17 years of age.
- 2) Maintenance of healed EE and relief of heartburn in pediatric patients 1 to 11 months of age and 12 to 17 years of age.
- 3) 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 maintenance of healed EE and relief of heartburn because the studies were not expected to be completed in time for the applicant 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.

## **10) Other Relevant Regulatory Issues**

*Financial Disclosures*

The applicant adequately disclosed financial arrangements with the clinical investigators. These arrangements do not raise concern over the integrity of the data. One investigator, (b) (4) who participated in Study TAK-390MR\_206 disclosed financial interests/arrangement under 21 CFR 54.2(a), (b), (c) and (f) as receiving significant payments of other sorts. This investigator's clinical study site was inspected by the Office of Scientific Investigations, who determined that the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. For Study TAK-390MR\_207, no investigators were reported to have financial interests/arrangements as defined by 21 CFR 54.2(a), (b), (c) and (f). See clinical review, by Dr. T. Altepeter, for full details.

*Office of Scientific Investigations*

The clinical reviewer selected four clinical site for inspection, predominantly based on their high enrollment rate or participation in more than one study. There were no specific compliance concerns for this application. For full details, refer to the Clinical Inspection Summary/Establishment Inspection Reports, by Dr. S. Leibenhaut. I have summarized the findings below.

Four clinical investigator (CI) sites were inspected for this application. One CI site has a final classification of voluntary action indicated (VAI) and the violations cited are not considered to have an impact on data integrity. The three other clinical site inspections have classifications of no action indicated (NAI). The studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication. The table below, reproduced from the Clinical Inspection Site Summary memo by Dr. S. Leibenhaut, dated 4/6/2016, lists the clinical sites that were inspected and summarizes the findings. The table below has been adapted from her review. Note that all inspection results at the time of the writing of this CTDL review have been finalized and the letters documenting this were entered into DARRTS between June 16 and 20, 2016.

Table 4: Clinical Inspection Results by Study Site

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # / # of Subjects	Inspection Date	Classification
Benjamin Gold, M.D. Site #7036 993-D Johnson Ferry Road, NE Atlanta, GA 30342	TAK-390MR_206/ 7 Subjects	December 10 to 22, 2015	VAI
Peter Winkle, M.D. Site #7020 1085 N. Harbor Blvd Anaheim, CA 92801	TAK-390MR_206/ 19 Subjects TAK-390MR_207/ 3 Subjects	January 5 to 14, 2016	NAI
Jaroslaw Kierkus, M.D. Site #7056 Al. Dzieci Polskich 20 Warszawa, Poland	TAK-390MR_207/ 12 Subjects	February 15 to 18, 2016	NAI
Bartosz Korczowski, M.D. Site #7058 Ul Lwowska 60 Rzeszow, Poland	TAK-390MR_207/ 12 Subjects	February 8 to 11, 2016	NAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

(source: adapted/updated based on the Clinical Inspection Summary, Dr. S. Leibenhaut, dated 4/6/2016)

The violations noted for Dr. Benjamin Gold are considered isolated and do not have a significant impact on subject safety or data integrity. For all study sites that were inspected, there were no limitations to the inspection. There was no evidence of under-reporting of adverse events. There were no discrepancies between the data in the line listings and the source documents except as noted concerning the date of last dose of study drug (SD) for Dr. Peter Winkle’s site where the dates of the last dose were unknown and the sponsor estimated 6 months from screening, which resulted in a date later than the discontinuation date. Overall, the reviewers concluded that the studies appear to have been conducted adequately, and the data generated by these sites may be used in support of the respective indication.

## 11) Labeling

### 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.

### *Highlights*

- In this section and throughout the label, the term [REDACTED] <sup>(b) (4)</sup> was replaced with “pediatric patients 12 years of age and older” to more clearly define the age group.
- The adverse reactions were revised to be consistent with Section 6.
- Aligned the language for the indications with the subheadings in the body of the prescribing information.

### *Section 1 Indications and Usage*

- The approved indications for Dexilant and Dexilant SoluTab were revised to include pediatric patients 12 year of age and older.

### *Section 2 Dosage and Administration*

- The duration of the pediatric trials was specified to state that pediatric trial duration for the maintenance of healed EE did not extend beyond 16 weeks in patients 12 years of age and older.

### *Section 6 Adverse Reactions*

- Section 6.1 Clinical Trials Experience was updated to include adverse reactions reported from the pediatric trials conducted in patients 12 years of age and older.

### *Section 8 Use in Specific Populations*

- A statement was added to clarify that the safety and effectiveness of dexlansoprazole has been established in pediatric patients 12 to 17 yes of age.

### *Section 12 Clinical Pharmacology*

- The section was revised to be consistent with the Clinical Pharmacology Labeling Guidance.
- Clinical pharmacology data relevant to dexlansoprazole in pediatric patients 12 to 17 years of age was added throughout the section.

### *Section 14 Clinical Studies*

- A statement was added to specify that the use of dexlansoprazole in this age group is supported by evidence from adequate and well-controlled studies of dexlansoprazole delayed-release capsules in adults, and is supported by safety and pharmacokinetic studies performed in pediatric patients.
- The details of the description of the clinical trial data were revised to more accurately reflect the data.
- The clinical trials results were revised to present both the ITT analysis and the pre-specified completer analysis. Given that the completer analysis, as pre-specified, may introduce bias (by selecting for patients who underwent endoscopy), the review team determined that the ITT analysis, allowing patients who had an endoscopy at time they discontinued the trial to be imputed, should also be presented. I agree that both the pre-specified completer analysis and the ITT analysis should be described in the label for the pediatric trials because 1) the completer analysis was utilized in the adult trials, despite the difference in approach to early discontinuations; however, given the timing of the endoscopies performed in the early discontinuations, it appears reasonable in this

situation to include the data, and 2) the ITT analysis is the preferred analysis to minimize the potential for bias.

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 approval of NDA 22287/1226 to expand the indications for Dexilant (dexlansoprazole delayed-release capsules) to include pediatric patients 12 years of age and older for the following:

- Healing of all grades of erosive esophagitis
- Maintenance of healed erosive esophagitis and relief of heartburn.
- Treatment of symptomatic non-erosive gastroesophageal reflux disease.

I recommend that the indications for Dexilant SoluTab be expanded to include pediatric patients 12 year of age and older for the following:

- Maintenance of healed erosive esophagitis and relief of heartburn.
- Treatment of symptomatic non-erosive gastroesophageal reflux disease.

### **Risk Benefit Assessment**

In support of this NDA, the applicant conducted two clinical safety and efficacy trials in pediatric patients 12 to 17 years of age to support product labeling for the healing of erosive esophagitis, maintenance of healed erosive esophagitis and relief of heartburn, and treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

I agree with the reviewers that the data submitted in the supplemental NDA establish safety and efficacy in pediatric patients 12 to 17 years of age, and the use of dexlansoprazole in this age group is supported by evidence from adequate and well-controlled trials of dexlansoprazole capsules in adults, and by safety and pharmacokinetic studies performed in pediatric patients.

### **Study 206**

The data from the single-arm, open-label, multi-center trial of 104 pediatric patients 12 to 17 years of age with symptomatic non-erosive GERD who were treated with dexlansoprazole delayed-release capsules 30 mg once daily for 4 weeks support the approval and product labeling of dexlansoprazole delayed-release capsules 30 mg for the treatment of symptomatic non-erosive GERD (sGERD) in this pediatric population. Patients with a documented history of GERD symptoms for at least three months prior to screening, reported heartburn on at least 3 out of 7 days during screening, and no esophageal erosions as confirmed by endoscopy were eligible for enrollment into the trial. The primary outcome was safety, defined as treatment

emergent adverse events (TEAEs) observed in  $\geq 5\%$  of patients. The secondary outcome (primary efficacy endpoint) was the percentage of 24 hour periods without daytime or nighttime heartburn.

At baseline, patients reported a median of 14% of days with neither daytime nor nighttime heartburn. During the 4-week treatment period, the median percentage of days with neither daytime nor nighttime heartburn improved to 47%. This result is generally similar to the results from the adult trials that supported product labeling. In the adult trials, the median percentage of 24-hour heartburn-free periods during the 4-week treatment period was 55% in the dexlansoprazole 30 mg arm and 19% in the placebo arm.

The single arm, open-label trial is not an ideal trial design even in the setting of extrapolation of efficacy from adequate and well-controlled trials conducted in adults to support the pediatric indication of treatment of sGERD. The rationale to support extrapolation is based on sufficiently similar pathophysiology of sGERD between adults and pediatric patients 12 to 17 years of age, and the similarity of disease progression and response to intervention. Based on the results of pharmacokinetic (PK) studies, the exposure between adults and pediatric patients 12 to 17 years of age is similar. Pharmacodynamic data (e.g., intragastric pH) were not collected during the pediatric trials in this age group (12 to 17 years of age), but the Division previously determined that for this age group, patient reported symptoms (i.e., heartburn), collected by age-appropriate questionnaires, can be used to compare efficacy with similar measures used in the adult trials. The dose selection in this pediatric trial is informed by PK similarity to adults and the efficacy results of the trials conducted in adults with sGERD. Dexlansoprazole 30 mg is the approved dose for adults for the treatment of sGERD; in the adult trials that supported labeling and approval, no additional clinical benefit was observed with doses higher than 30 mg for the treatment of sGERD. The dose selected for this pediatric trial appears reasonable for the treatment of sGERD. In addition, dexlansoprazole is the sixth in class for proton pump inhibitors (PPI); the totality of data collected from multiple products from both adult and pediatric trials in this class of drugs provides an understanding of the mechanism of action to support the efficacy of PPI therapy for the treatment of symptomatic non-erosive GERD. Therefore, there is a substantial level of confidence in the data to support extrapolation of efficacy from adult data for the treatment of symptomatic non-erosive GERD in pediatric patients 12 to 17 years of age. For the reasons described above, the use of dexlansoprazole in pediatric patients 12 to 17 years of age is supported by evidence from adequate and well-controlled trials of dexlansoprazole delayed-release capsules in adults, and by safety and pharmacokinetic studies performed in pediatric patients.

### **Study 207**

The data from the multi-center, 36-week trial in 62 patients 12 to 17 years of age with a documented history of GERD for at least three months and endoscopically-proven erosive esophagitis (EE) evaluated the healing of EE, maintenance of healed EE and relief of heartburn to support approval and product labeling for the healing of all grades of EE, maintenance of healed EE and relief of heartburn in this pediatric population. This trial design included an 8-week open-label phase to evaluate the safety and effectiveness of dexlansoprazole delayed-release 60 mg capsules daily for the healing of EE, followed by a randomized withdrawal, double-blind, placebo controlled 16-week phase in patients with

healed EE to evaluate the safety and effectiveness of dexlansoprazole delayed-release 30 mg capsules or placebo for the maintenance of healed EE and relief of heartburn. The trial also included an additional 12 week follow-on phase without treatment for patients who maintained healing during the double-blind phase.

Of the 62 patients enrolled, 58 patients completed the 8 week open-label phase to evaluate for the healing of EE. Fifty-one of fifty-eight (88%) patients who completed and underwent post-baseline endoscopy achieved healing of EE over 8 weeks of treatment. In the adult trials that supported product labeling, 85% and 87% of adults from two adequate and well-controlled trials, respectively, achieved healing of EE at week 8. Of note, the applicant adhered to the pre-specified analysis to calculate the proportion of patients with healed EE at week 8, which was calculated by the number of patients who were healed divided by the number of patients who had available post-baseline endoscopy data. Of the 62 patients enrolled, 4 patients discontinued early and none had an endoscopy performed at the time of discontinuation. When these 4 patients were included in the analysis, the proportion of patients with healed EE decreases slightly to 51/62 (82%) patients with healing of EE. The overall conclusions remain unchanged given the high proportion of patients who completed the 8 weeks and had documented healing of EE.

After the initial eight weeks of treatment, 51 patients with healed EE, confirmed by endoscopy, were randomized to receive treatment with dexlansoprazole 30 mg capsules or placebo, once daily for an additional 16 weeks of treatment. Thirty-eight patients completed the 16 weeks of maintenance therapy, and 46 patients had endoscopy data available for the efficacy analysis (8 patients discontinued early but underwent post-baseline endoscopy). Of the 46 patients with post-baseline endoscopy data, 18/22 (82%) patients in the dexlansoprazole group and 14/24 (58%) patients in the placebo group remained healed, confirmed by endoscopy, over the 16 week treatment period. In the adult trials that supported product labeling, the maintenance of healed EE was achieved in 66% of patients in the dexlansoprazole 30 mg arm and 14% of patients in the placebo arm; patients with at least one post-baseline endoscopy were included in the analysis.

Of note, the applicant adhered to the pre-specified analysis to calculate the maintenance of healed EE at week 24; however, this analysis is consistent with a “completer analysis” rather than an ITT analysis, which at the time of this review, is the preferred method for analysis of the efficacy endpoints. The pre-specified analysis is calculated by the number of patients who maintained healing divided by the number of patients who have available post-baseline endoscopy data. Of the 13 patients who withdrew during the double-blind maintenance phase, the analysis includes 8 patients (4 patients in the dexlansoprazole group and 4 patients in the placebo group) who discontinued treatment prior to week 24 but have available endoscopy data, and excludes 5 patients (2 patients on placebo, 3 patients on dexlansoprazole) who discontinued early and did not have available endoscopy data. The pre-specified analysis used in the pediatric trials was generally similar to the analysis utilized in the trials that supported approval in the adult population, in which patients who had at least one post-baseline endoscopy. Therefore, to facilitate comparisons to the adult efficacy data, it seems reasonable to use the same analysis methods.

However, a difference exists between the pediatric and adult trials in the approach to handling early discontinuations. In the adult trials, adult patients who discontinued early were considered as treatment failures even if the endoscopic findings were consistent with healed EE, whereas in the pediatric trials, patients who discontinued early and had available endoscopy data were imputed. Of the 8 patients who discontinued the treatment prior to week 24 and were included in the efficacy analysis, only 2 patients in the placebo group maintained healing and 1 patient in the dexlansoprazole group maintained healing. The review team evaluated the timing of when the endoscopy was performed for the patients who discontinued early to determine whether inclusion of these patients could affect the outcome of the trial. Given that the patients who discontinued early underwent endoscopy at a time point that approximated the week 24 assessment, it is reasonable to include the patients with endoscopy data into the analysis, taking into account the timing of the endoscopies, small sample size, descriptive nature of the analyses, and the clinical importance of the endoscopic findings to inform whether patients 12 to 17 years of age benefit from continued maintenance therapy after the initial healing of EE.

When a sensitivity analysis (ITT analysis) was performed by the review team, the proportion of patients who maintained healing of EE decreased slightly to 18/25 (72%) in the dexlansoprazole group and 14/26 (54%) in the placebo group. This ITT analysis includes 5 patients who were early discontinuations from the trial and did not undergo endoscopy; therefore, are counted as treatment failures. Using a more conservative approach, similar to the handling of early discontinuations in the adult trials, where the 3 patients who discontinued early and had documentation of healing were counted as treatment failures instead of responders, the proportion of patients who maintained healing decreases further to 17/25 (68%) patients in the dexlansoprazole group and 12/26 (46%) in the placebo group. While the proportion of patients who maintained healing decreases in both the dexlansoprazole and placebo groups, the overall conclusions remain unchanged as the proportion of patients who maintained healing of EE remains comparable to the adult data. There is a substantial level of confidence in the evidence to support extrapolation of efficacy in this indication for the pediatric population 12 to 17 years of age. For future trials, I recommend using an ITT analysis with the completer analysis as supportive given that the completer analysis may introduce bias since it selects for patients who underwent endoscopy. I agree with the review team that both the pre-specified completer analysis and the ITT analysis should be described in the label for the pediatric trials because 1) the completer analysis was utilized in the adult trials, despite the difference in approach to early discontinuations; however, given the timing of the endoscopies performed in the early discontinuations, it appears reasonable in this situation to include the data, and 2) the ITT analysis is the preferred analysis to minimize the potential for bias.

The high placebo rate observed in the pediatric trial was also considered in the context of determining whether maintenance therapy is necessary in pediatric patients 12 to 17 years of age. There were differences between the pediatric and adult trials with respect to the baseline severity of esophagitis and duration of treatment that may have contributed to the divergent placebo rates. The adult trials evaluated the maintenance of healing at 6 months, as compared to at 4 months in the pediatric trial. Upon review of the adult data, it was noted that the placebo rate declined over time based on results from endoscopy performed at 1 month, 3

months, and 6 months. The higher placebo rate at earlier time points and the decline over time suggests that the placebo rate in pediatric patients may have also declined between month 4 and month 6. Additionally, the pediatric patients overall had less severe disease (97% Los Angeles Classification Grades A/B) as compared to the adult patients (71% Los Angeles Classification Grades A/B), which may also contribute to the higher placebo rate observed during the maintenance phase in the pediatric patients once initial healing of EE was achieved. In fact, the healing rate and maintenance of healing rates were numerically greater in patients with Grade B esophagitis who were treated with dexlansoprazole compared to placebo (9/11 [82%] vs 1/8 [13%]). There were an insufficient number of patients with grades C-D to determine whether differences exist based on initial LA grade. There was one patient with grade C esophagitis at baseline who healed at week 8, and was later randomized to placebo; however, this patient did not maintain healing to week 24. The one patient with grade D at baseline did not heal at week 8, but showed improvement to Grade B after 8 weeks of therapy. While the trial was not adequately powered, the inclusion of the placebo arm allows for a descriptive comparison between dexlansoprazole and placebo to evaluate the benefit of maintenance therapy after healing of EE has been achieved. The data suggest that there may be a subset of patients who benefit from maintenance therapy, including patients with more severe disease.

In addition to the healing of EE and maintenance of healed EE, the proposed indication also includes relief of heartburn. During the 16-week maintenance period, the median percentage of days with neither daytime nor nighttime heartburn was 14% at baseline, increased to 66% over the initial 8-week healing phase, and further increased during the 16-week maintenance phase to 87% for patients receiving dexlansoprazole 30 mg compared to 68% on placebo. While the placebo group reported a high rate of heartburn-free days, the patients were not largely symptomatic at the start of the maintenance phase, suggesting that the relief of heartburn symptoms is more closely associated with the initial healing of EE but the data support that symptoms remained well-controlled during the maintenance phase. In addition, there was minimal change from baseline during the maintenance phase in the placebo group whereas the dexlansoprazole group experienced further benefit for the control of heartburn.

Out of the 32 patients who maintained healing of EE at the end of the 16-week maintenance period, 27 patients (16 treated with dexlansoprazole and 11 treated with placebo in the double-blind phase) were followed for an additional 12-weeks without therapy. Twenty-four of the 27 patients completed the 12-week follow-up. One patient required treatment with acid suppression therapy, which suggests that therapy may be discontinued in most pediatric patients once the EE is treated adequately.

The trial was designed to assess whether there was a need for long-term treatment to maintain healing of EE in pediatric patients 12 to 17 years of age. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) clinical practice guidelines state that “not all reflux esophagitis is chronic or relapsing.”<sup>6</sup> Further, the

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<sup>6</sup> Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for

guidelines do not endorse continuation of PPI therapy beyond 3 to 6 months of treatment, and recommend discontinuation of therapy once a patient has been asymptomatic for a sufficient duration to minimize exposure to unnecessary lengths of treatment. Based on the results of study 207 provided in this supplemental NDA, the data suggest that long-term therapy may not be required in all patients and discontinuation of therapy may be considered once the esophagitis is adequately healed.

It is notable that the applicant included a double-blind, placebo controlled, randomized withdrawal 16-week maintenance phase in this pediatric trial. While the trial was not adequately powered and the results of the analyses are descriptive, the inclusion of the placebo arm allows for a comparison of dexlansoprazole to placebo to better inform whether maintenance therapy is necessary in pediatric patients 12 to 17 years of age.

Based on the reasons described in this document, the use of dexlansoprazole in this age group is supported by evidence from adequate and well-controlled trials of dexlansoprazole capsules in adults, and by efficacy, safety and pharmacokinetic studies performed in pediatric patients.

The adverse event profile was generally comparable between adults and pediatric patients 12 to 17 years of age, and were consistent with the known safety profile of dexlansoprazole delayed-release capsules.

Based on the totality of the data, I agree with the reviewers that dexlansoprazole should be approved for the indications of healing of erosive esophagitis, maintenance of healed erosive esophagitis and relief of heartburn, and treatment of symptomatic non-erosive gastroesophageal reflux disease in pediatric patients 12 year of age and older. 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 pediatric trials conducted to support labeling in pediatric patients 12 to 17 years of age utilized Dexilant delayed-release capsules; however, the labeling for patients 12 years and older will apply to both the Dexilant and Dexilant SoluTab. Dexilant SoluTab 30 mg was approved based on the establishment of bioequivalence to the Dexilant 30 mg capsule. The pediatric assessments submitted in this supplemental NDA will serve to fulfill the PREA PMRs for the pediatric indications in the 12 to 17 year age group for the following:

Dexilant (NDA 22287)

1356-5            Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years.

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Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). Vandenplas Y., et al. J Pediatr Gastroenterol Nutr. 2009 Oct;49(4):498-547.

1788-1            Deferred study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 12 years to 17 years of age.

Dexilant SoluTab (NDA 208056)

3019-2            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.

3019-4            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.

**Recommended Comments to Applicant**

No additional comments to the applicant are recommended at this time.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JULI A TOMAINO  
07/01/2016