Clinical Review

Application Type	Pediatric efficacy supplement to expand the indications to include pediatric patients ≥ 12 years of age
Application Number	sNDA 22287 / SD 1226
Priority or Standard	10 month standard
Submit Date(s)	September 30, 2015
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PDUFA Goal Date	July 29, 2016
Division / Office	Gastroenterology and Inborn Errors Products
Reviewer Name(s)	Tara Altepeter, MD
Review Completion Date	June 23, 2016
Established Name	Dexlansoprazole
(Proposed) Trade Name	Dexilant
Therapeutic Class	Proton Pump Inhibitor
Applicant	Takeda
Formulation(s)	Delayed release capsule
Dosing Regimen	30mg daily or 60mg daily
Indication(s)	Healing of all grades of erosive esophagitis (EE), to maintain healing of EE and relief of heartburn, treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).
Intended Population(s)	Pediatric patients 12-17 years of age

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer considers NDA 22287, supplements 21, 22 and 23 for Dexilant (dexlansoprazole delayed release capsules) to be acceptable to recommend approval of Dexilant (dexlansoprazole delayed-release capsules) for the treatment of pediatric patients 12 to 17 years of age. This reviewer agrees with the applicant's proposal to expand the current indications of Dexilant, including treatment of heartburn associated with symptomatic non-erosive GERD (sGERD), healing of all grades of erosive esophagitis (EE), and to maintain healing of EE and relief of heartburn, to include pediatric patients 12 to 17 years of age. Safety and efficacy data from two clinical trials (studies 206 and 207) were included in the submission and will be reviewed in this document. To support approval, efficacy was partially extrapolated from adult data. In both symptomatic non-erosive gastroesophageal reflux disease (sGERD) and erosive esophagitis (EE), the disease progression and response to intervention are sufficiently similar between adults and pediatric patients 12 years of age and older to facilitate partial extrapolation of efficacy. Further, there is similarity between the PK profiles of adults and pediatric patients 12 to 17 years of age. The safety and efficacy were overall similar to the data from the adult trials which supported approval. Therefore, this reviewer recommends approval of sNDA 22287/SD 1226 that will expand the current indications to include 12 to 17 year olds. Of note, given that Dexilant SoluTab 30 mg was approved based on bioequivalence to Dexilant delayed-release capsules, the approved indications for Dexilant SoluTab (treatment of heartburn associated with symptomatic non-erosive GERD and to maintain healing of EE and relief of heartburn) will also be expanded to include pediatric patients 12 to 17 years of age.

1.2 Risk Benefit Assessment

The applicant proposes to expand the current indications for Dexilant, 30 mg and 60 mg capsules, and Dexilant SoluTab, 30 mg orally disintegrating tablet, to include pediatric patients 12 to 17 years of age. The currently approved indications for Dexilant include treatment of heartburn associated with symptomatic non-erosive GERD (sGERD), healing of all grades of erosive esophagitis (EE), and to maintain healing of EE and relief of heartburn. The currently approved indications for Dexilant SoluTab include treatment of heartburn associated with symptomatic non-erosive GERD (sGERD), and to maintain healing of EE and relief of heartburn. Dexilant 30 mg daily is proposed for treatment of sGERD in patients 12 to 17 years of age. The adverse events noted in study 206 are consistent with the known safety profile of Dexilant in adults, and consistent with what is known about this class of medications overall. Adverse events that were seen in ≥5% of patients in this open label trial included abdominal pain, diarrhea, and headache. Efficacy was demonstrated by the median percentage of

heartburn free 24 hour periods, which was 47% in this population (compared with 55% in the adult trials). The data demonstrate that the risk from Dexilant is no greater than that reported for other proton pump inhibitors, and symptomatic benefit is demonstrated. This reviewer thus recommends approval of this indication.

Dexilant 60mg daily for 8 weeks is proposed for the healing of erosive esophagitis (EE), and Dexilant 30mg daily for an additional 4 months is proposed to maintain healing of EE and control heartburn symptoms in pediatric patients aged 12 to 17 years. Efficacy in healing of EE was demonstrated, with 88% of patients healed by week 8 in the open label trial (similar to healing seen in adults). For maintenance of healing, patients who received the four additional months of treatment did better (82% maintained healing) compared with those who received placebo (58%). The adverse events reported in study 207 were also consistent with the known safety profile.

In study 207, the adverse events seen in ≥5% of patients and more commonly on treatment than placebo included headache, oropharyngeal pain, nasopharyngitis, abdominal pain, diarrhea, pharyngitis and respiratory tract infections.

There were no new safety signals identified in these two pediatric trials. The exposure was sufficient to assess for common adverse events when the drug is used as directed. However, this reviewer notes that the small sample size and short duration of these trials may limit their ability to identify rare but serious adverse events, or those associated with prolonged use over many years. Known serious adverse events associated with Dexilant are class specific, and are included in the current product labelling. These include acute interstitial nephritis, vitamin B-12 deficiency, increased risk of clostridium difficile associated diarrhea, osteoporosis related bone fractures, and hypomagnesemia. With the exception of acute interstitial nephritis, these adverse events are associated with much longer term use (years, rather than months) than is recommended for pediatric patients. Refer to section 1.4 below regarding outstanding post-marketing requirements.

In summary, Dexilant was well tolerated in these pediatric trials, and no new information emerged which would alter the risk benefit assessment that supported initial approval in adults. This reviewer concludes that the benefits from use of Dexilant in the treatment of heartburn associated with sGERD, healing of EE, and to maintain healing of EE and relieve heartburn in pediatric patients 12 to 17 years outweigh the known risks, and approval is recommended.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The trials submitted with this application provided safety data specific to the recommended duration of treatment (4 weeks for treatment of sGERD, 8 weeks for healing of EE, and 4 months for maintenance of healing of EE). However, these data do not allow for adequate assessment of the risk of long term use of Dexilant in pediatric patients. A subset of patients with underlying conditions predisposing them to more severe and persistent GERD and/or EE may require long term and ongoing treatment. The following post marketing requirement is outstanding to assess the safety of Dexilant in this population:

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.

No additional post-marketing requirements or commitments are recommended based on this review.

2 Introduction and Regulatory Background

Gastroesophageal reflux disease (GERD) comprises a spectrum of acid-related disorders, including nonerosive GERD and erosive esophagitis (EE). Nonerosive GERD is defined as the presence of symptoms caused by intraesophageal acid reflux in patients with absence of endoscopically observed injury to the esophageal mucosa. Erosive esophagitis is defined as the presence of superficial esophageal erosions in patients with or without typical GERD symptoms.

Erosive esophagitis is diagnosed during endoscopy in up to 50% of patients with GERD symptoms.[1] The severity of these symptoms is associated with the extent and duration of gastric acid exposure in the esophagus, as well as the presence of pepsin. Patients who do not receive treatment, or in whom acid reflux is not effectively controlled, are at risk of developing significant complications, such as bleeding, strictures, and the premalignant condition of Barrett's esophagus.

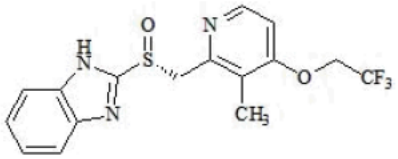
Therapy for GERD and related complications is largely focused on reduction of esophageal exposure to acid material, either by pharmacological or surgical means, with surgery usually reserved for intractable cases. Pharmacological management of GERD includes treatment with antacids, histamine$_2$-receptor antagonists, prokinetic

1 Fennerty M. Medical treatment of GERD in the managed care environment. *Semin Gast Dis* 8: 90-99; 1997.

agents, and proton pump inhibitors (PPIs). PPIs, which are labeled for once daily (QD) dosing, are the most effective medications for relieving GERD symptoms, healing the injured mucosa, maintaining a healed mucosa, and preventing the development of complications.

2.1 Product Information

Dexilant (dexlansoprazole)



Dexilant (dexlansoprazole delayed release capsules) is the R-enantiomer of lansoprazole, a proton pump inhibitor. Proton pump inhibitors suppress gastric acid secretion by irreversible blockade of the H+/K+ ATP-ase on gastric parietal cells. The R-enantiomer was shown to have a prolonged pharmacokinetic and pharmacodynamic profile, compared with the racemic mixture. The product contains two types of granules, designed with different pH-dependent release profiles. Approximately (b) (4) of the drug is released within (b) (4) of ingestion, and the remaining (b) (4) of the dose is released within (b) (4) of ingestion.

Dexilant is currently approved in adults for:

- Healing of all grades of erosive esophagitis (EE).
- To maintain healing of EE and relief of heartburn.
- Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

In this efficacy supplement, the applicant proposes to expand the above indications to the adolescent age group, patients aged 12 – 17 years, inclusive.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently approved treatments for pediatric GERD

Drug	Approved for Pediatrics, ages:
Ranitidine	1 month to 16 years
Famotidine	Birth to 16 years
Omeprazole	1 year to 16 years
Lansoprazole	1 year to 17 years
Pantoprazole	5 years to 16 years
Esomeprazole	1 month to 17 years
Rabeprazole	1 year to 17 years

(source: reviewer's table, created from approved product labels for each product; available at Drugs@FDA website, http:accessdata.fda.gov/scripts/cder/drugsatfda)

For the treatment of pediatric GERD, there are 2 histamine receptor antagonists (ranitidine and famotidine), and 5 proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole) currently approved for use in patients 12 to 17 years of age. If approved for use in patients 12 to 17 years of age, Dexilant will be the sixth PPI indicated in this population. Pediatric GERD has historically been described in product labelling to include patients with and without erosive esophagitis. More recently the indications of non-erosive GERD and erosive esophagitis have been described separately. Refer to approved product labelling for each product for additional details. All currently approved PPIs are indicated for the healing of EE. Omeprazole is currently the only available PPI specifically labelled for maintaining remission of EE in pediatric patients.

2.3 Availability of Proposed Active Ingredient in the United States

Dexilant (dexlansoprazole) is manufactured by Takeda Pharmaceuticals. Dexilant (dexlansoprazole delayed-release capsule) was originally approved January 30, 2009 under the name Kapidex. The proprietary name was later changed to Dexilant, which is the name used in labelling after March of 2010.

Dexilant 30 mg and 60 mg delayed-release capsules have been available in the United States since original approval of the drug in 2009 for the following indications in adults:

- Healing of all grades of erosive esophagitis (EE)
- To maintain healing of EE
- Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

An efficacy supplement, approved on June 17, 2011, expanded the indication for maintaining healing of EE to include the relief of heartburn. Refer to Section 2.5 below for detailed regulatory history of the product.

Dexlansoprazole is also currently available as Dexilant SoluTab (dexlansoprazole delayed-release orally disintegrating tablets [ODT]) 30 mg, approved on January 26, 2016 for the following indications in adults:

- To maintain healing of EE and relief of heartburn
- Treatment of heartburn associated with sGERD.

2.4 Important Safety Issues With Consideration to Related Drugs

Safety concerns specific to the proton pump inhibitor drug class have come to light over the last decade including increased risk of *Clostridium difficile* infection, decreased bone mineral density and related risk of fractures, acute interstitial nephritis, vitamin B12 deficiency (particularly with prolonged use >3 years), hypomagnesemia, and most recently, (b) (4) These events are described in section 5, Warnings and Precautions, in the approved product label for Dexilant.

The increased risk of cardiovascular events in patients on PPI is hypothesized to occur due to drug-drug interactions between PPI and clopidogrel, both metabolized through the hepatic cytochrome P450 system. There are no randomized controlled trials looking at this issue, and various observational studies have shown conflicting results. A recent systematic review, published in Journal of the American Heart Association in 2015, attempted to categorize the risk of adverse cardiac outcomes among patients recently discharged after a diagnosis of acute coronary syndrome, on both a PPI and clopidogrel. The authors determined that pantoprazole, lansoprazole, and esomeprazole were associated with adverse CV outcomes, though the data did not show this association for omeprazole.[2] (b) (4)

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

With the original approval of Dexilant on January 30, 2009, the following Pediatric Research Equity Act (PREA) postmarketing requirements (PMR) 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 EE in pediatric patients 1 year to 11 years (modified 6/17/2011).

2 Sherwood, MW, Melloni C, Jones WS, et al. Individual proton pump inhibitors and outcomes in patients with coronary artery disease on dual antiplatelet therapy: a systematic review. J Am Heart Assoc. 2015; 4:e002245. DOI 10.1161/JAHA.115.00245

- **1356-2: Deferred pediatric study under PREA for healing and maintenance of healing of all grades of EE in pediatric patients 12 years to 17 years (modified 6/17/2011).**

- 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 02, 2009
A Type C meeting was held to discuss changes to the proposed clinical studies in patients 12-17 years of age with erosive esophagitis and symptomatic GERD. Agreements were made on the proposed (b) (4) overall study design, and doses to evaluate the safety and effectiveness of dexlansoprazole in pediatric patients 12 -17 years of age. To address the issue of maintenance of healed EE, the applicant provided a literature review to support the claim that PPI therapy should be used for maintenance of healed EE. The Division advised the applicant that clinical data would still be necessary to assess safety for the expected duration of treatment.
Refer to the final meeting minutes, dated 12/9/2009, for full details.

June 17, 2011
An efficacy supplement was approved that expanded the indication of maintaining healing of erosive esophagitis to include the relief of heartburn. The PREA deferred studies were modified to allow for better assessment of whether there was a need to continue therapy for the maintenance of 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 evaluate pediatric patients with predisposing factors for chronic gastroesophageal reflux disease and erosive esophagitis who require chronic treatment with dexlansoprazole. The revised and new PREA required studies are listed below.

- **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.

It should be noted that there were no modifications to PREA Study 1356-5 at the time of efficacy supplement approval.

December 14, 2011

A Type C meeting was held to discuss the amended protocols designed to address the PREA PMRs for 12 to 17 year old patients. During that meeting the Division agreed with the overall proposed study design, with the following suggested revisions:

- The Division recommended that 8 weeks should be the treatment duration to assess healing of EE, to be in line with adult studies. Takeda agreed, and clarified that those not healed at 8 weeks would be dropped from study and would receive standard of care treatment.
- Takeda provided information to support that changes to the eDiary were completed to ensure age-appropriateness.
- The Division proposed that patients be followed for at least 3 months after completing the treatment phase of study 207, Takeda agreed to submit proposal for this.
- The Division expressed agreement with planned dosages to be studied.
- Takeda agreed to collect sample for genotyping of all patients for CYP2C19 to explore correlation with safety and efficacy.
- Takeda agreed to 24 hr urine collection for urinary magnesium excretion for any patient that develops hypomagnesemia during the study.

March 5, 2012

- Final protocol for study TAK-390MR_207 entitled “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. (In this document, study TAK-390MR_207 will be referred to as "study 207").

- Final protocol for study TAK-390MR_206 entitled "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. (In this document, study TAK-390MR_206 will be referred to as "study 206").

2.6 Other Relevant Background Information

Dexilant was approved in 16 European countries via the decentralised procedure in September 2013. It is also currently marketed in Canada, as well as across Southeast Asia.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was acceptable for review. It was complete and well-organized. All electronic information was readily available.

3.2 Compliance with Good Clinical Practices

The applicant stated that the clinical trials were conducted in accordance with the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC), and in accordance with United States and international standards of Good Clinical Practice (GCP) as defined by the Food and Drug Administration [FDA] Title 21 part 312 and International Conference on Harmonization [ICH] guidelines.

After consultation with the Office of Scientific Investigations (OSI), two sites from each clinical study were selected for inspection. Sites were chosen based on results from standardized site selection tool, with additional input from OSI, to ensure integrity of data and adherence to protocol policies and Good Clinical Practice. The clinical site inspection final reports are outstanding at the time this review.

Protocol Deviations:

Study 206 (symptomatic GERD):

Of 104 patients enrolled, 63 patients had at least one protocol deviation. The most common reasons for protocol deviations included procedure not performed per protocol (34 occurrences), and deviations related to entry criteria (29 occurrences). The deviations related to entry criteria were generally related to deviations from scheduled procedures (e.g., delay in receipt of screening labs, delay in obtaining appropriate signatures on ICF, etc), rather than enrollment of patients who did not meet disease criteria that may have an impact on the results of the study. The specific violations in inclusion/exclusion criteria are summarized in Table 2 below.

Table 2: Violations in Inclusion/Exclusion Criteria (study 206)

Patient Number	Inclusion/Exclusion Criteria violated
7011-003	Took PPI within 7 days of screening
7036-001	Took PPI within 7 days of screening, celiac screening results not available prior to enrollment, history of GI surgery (pyloromyotomy)
7036-004	Took PPI within 7 days of screening, celiac screening results not available prior to enrollment, required or anticipated to require a disallowed concomitant medication (not on stable dose of amitriptyline)
7036-005	Took PPI within 7 days of screening
7051-004	Failed to meet inclusion criteria of symptoms of heartburn present on at least 3 of any 7 days
7055-002	Failed to meet inclusion criteria of symptoms of heartburn present on at least 3 of any 7 days
7074-001	Failed to meet inclusion criteria of symptoms of heartburn present on at least 3 of any 7 days

(source: reviewer's table, created from data provided in applicant's sNDA22287 submission, received 9/30/2015, clinical study report for study 206 and Appendix 16.2.2.1)

The goal of study 206 was to demonstrate efficacy in relief of heartburn in patients with symptomatic non-erosive GERD. In the first four protocol violations described above, the violation is unlikely to have a meaningful impact the study results. The violations where a patient was administered a PPI within 1 week of starting treatment may affect whether a patient qualifies for the study based on frequency of symptoms but would likely result in exclusion from the study as the prior PPI therapy may have relieved or mitigated the heartburn. Therefore, the patient would be less likely to meet symptom criteria for inclusion. Including patients with celiac disease or positive antibody test for celiac should not affect the presence of heartburn or response to treatment, as celiac disease affects the small bowel, and is not generally associated with heartburn symptoms. In addition, both of these patients were shown to be negative for celiac, when results were later obtained.

The three patients who were listed as not meeting inclusion criteria were recorded as having a protocol violation because the symptoms were not documented in the eDiary

using the pre-specified electronic method due to technical difficulties with the eDiary. However, these three patients had documentation of symptoms during the screening period via email or paper instead of the eDiary, and were confirmed to meet symptomatic inclusion criteria for symptoms on 3/7 days.

This reviewer assessed the remaining "significant protocol deviations" as described by the applicant in Appendix 16.2.2.2 of the sNDA submission. The majority were minor deviations that would be unlikely to affect clinical outcomes in a meaningful way, such as investigators incorrectly filling out ICF forms, problems with processing some laboratory specimens, a single dose of a prohibited medication given at screening endoscopy (such as dexamethasone or metoclopramide). Several patients were noted to have poor study drug compliance (patient 7074-001: 17% compliant, patient 7069-001: 71% compliant, patient 7060-002: 53% compliant, patient 7009-002: 35% complaint); however in the opinion of the reviewer, this represents real world difficulties with patient compliance with treatment. Furthermore, poor compliance would be unlikely to skew the results in favor of Dexilant since taking less than the prescribed amount of medication would likely result in decreased efficacy.

Study 207 (erosive esophagitis):
For the open-label treatment phase of study 207, there were 27/62 patients with at least one protocol deviation. The most common protocol deviation was related to procedure or assessment not done in accordance with the study timeline (19 occurrences).

For the placebo-controlled phase of the study, 23/51 patients had at least one protocol deviation. The most common reason for protocol deviations were related to the procedure or assessment not conducted in accordance with the study timeline (16 occurrences).

There was only one violation of inclusion/exclusion criteria. Patient 7056-009 was not excluded despite evidence of eosinophilic esophagitis at screening. This patient received 20 days treatment, but was discontinued when this result was obtained, and was not included in the efficacy analysis.

Based on the "significant protocol deviations" identified by the applicant, including poor compliance with the study drug or timing of laboratory procedures, the majority are unlikely to bias the results of the study in favor of Dexilant.
Overall the opinion of this reviewer is that the deviations are unlikely to significantly impact the overall outcomes of the trial.

3.3 Financial Disclosures

Financial disclosures were provided and reviewed.

The applicant adequately disclosed financial arrangements with the clinical investigators. These arrangements do not raise concern over the integrity of the data. Refer to Section 9.4 for further details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC data were submitted.

4.2 Clinical Microbiology

No new clinical microbiology data were submitted.

4.3 Preclinical Pharmacology/Toxicology

No new non-clinical studies were conducted.

4.4 Clinical Pharmacology

The clinical pharmacology review team concluded that the data provided in this application are sufficient to support the dosages proposed for patients 12 to 17 years of age. The doses selected were based on the results of previously performed dose finding trials in adults, and demonstrated PK similarity between adult and pediatric patients (described below in section 4.4.3)

4.4.1 Mechanism of Action

Dexilant is a proton pump inhibitor, which suppresses gastric acid secretion by irreversibly binding and inhibiting the H+/K+/ATP-ase pump located in gastric parietal cells. This results in an increase in intragastric pH, which is associated with decreased GERD symptoms and promotes healing of EE.

4.4.2 Pharmacodynamics

No new pharmacodynamic data was submitted with this application.

4.4.3 Pharmacokinetics

The results of study T-P107-163: “A Phase 1, Randomized, Open-Label, Parallel Group, Multicenter Study to Evaluate the Pharmacokinetics and Safety of Dexlansoprazole Modified Release Capsules (30mg and 60mg) in Adolescents with Symptomatic Gastroesophageal Reflux Disease” were submitted with this application.

Data from this study, comparing pharmacokinetic parameters in healthy adults to pediatric patients 12 to 17 years of age with sGERD demonstrated that exposure between adults and pediatric patients was similar. The data were used to inform the doses selected for study 206 and study 207.

Table 3 below summarizes the PK results for study TP107-163.

Table 3: PK parameters for patients 12 to 17 years of age compared with healthy adults

	N	Tmax (hr)	Cmax (ng/mL)	AUC(0-24) or AUC(0-tau)(a) (ng·hr/mL)	T1/2 (hr)	CL/F (L/hr)
Multiple 30 mg Dose – Subjects 12 to 17 Years of Age – Day 7 Data(b)						
Mean	17	4.65	691	2886	1.32(c)	12.8
%CV		63	53	47	52	48
Multiple 30 mg Dose – Healthy Adult Subjects – Day 5 Data(d)						
Mean	44	4.45	658.1	3275	1.49(c)	11.4
%CV		37	40	47	49	48
Multiple 60 mg Dose – Subjects 12 to 17 Years of Age – Day 7 Data(b)						
Mean	18	3.31	1136	5120	2.04(c)	15.3
%CV		46	51	58	53	49
Multiple 60 mg Dose – Healthy Adult Subjects – Day 5 Data(d)						
Mean	79	4.64	1396.7	6529.1	1.54(c)	11.6
%CV		46	51	60	52	46

(source: Table 13.a, applicant's clinical study report for study T-P107-163, page 60/63).

PK was compared between healthy adults and pediatric patients 12 to 17 years of age. Following administration of dexlansoprazole 30 mg daily, the mean C_{max} and $AUC_{(0\text{-}tau)}$ at steady state in pediatric patients were 691 ng/mL and 2886 ng.h/mL, respectively, and were 658 ng/mL and 3275 ng.h/mL, respectively in healthy adults. For the 60 mg daily dose, mean C_{max} and $AUC_{(0\text{-}tau)}$ at steady state in pediatric patients were 1136 ng/mL and 5120 ng.h/mL, respectively, and were 1397 ng/mL and 6529 ng.h/mL, respectively, in healthy adults.

Overall, individual C_{max} and AUC values in pediatric patients are similar to those observed in the adult patients. The clinical pharmacology team determined that this data are sufficiently similar to justify the dose selection for pediatric patients 12 to 17 years of age.

Refer to the clinical pharmacology review by Dr. Shen Li, dated June 13, 2016, for further details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Summary of Clinical Studies

Trial Name	Type	Objectives	Design	Dosage Regimen	Number Enrolled	Population	Duration of Treatment	Number of Centers	Countries involved
TK206	Phase 2, Open Label	-To assess safety and effectiveness of daily oral administration of dexlansoprazole delayed release capsules for relief of heartburn in adolescent patients 12 to 17yr with symptomatic non erosive GERD	Open-Label, multicenter, multinational	30mg once daily, oral	104 enrolled, 102 completed	Pediatric patients aged 12 to 17 years	4 weeks	36	Belgium, Brazil, Hungary, Italy, Mexico, Poland, Portugal, United States of America
TK207	Phase 2, Open Label	-To assess the safety and effectiveness of treatment with once daily oral administration of dexlansoprazole 60mg for healing erosive esophagitis in adolescent patients aged 12 to 17 years.	Initial phase- open label	30mg once daily, oral	62 enrolled, 58 completed open label phase	Pediatric patients aged 12 to 17 years	36 weeks	18	Mexico, Poland, Portugal, United States
	Double Blind, Placebo Controlled	-To assess safety and effectiveness of dexlansoprazole 30mg daily compared to placebo for the maintenance of healed erosive esophagitis and relief of heartburn in adolescent patients aged 12 to 17yr	Subsequent phase – randomized, placebo controlled	60 mg once daily, oral Placebo	51 were eligible to continue to maintenance phase, 38 completed				

(source: reviewer's table, created based on applicant's submitted final protocols for studies TAKMR_206 and TAKMR_207, sNDA 22287 application, received September 30, 2015)

5.2 Review Strategy

This review will focus on the safety and efficacy endpoints of these studies. Two studies were included in this sNDA submission and were the primary sources of clinical data reviewed in this document. Study 206 provides the clinical efficacy and safety data to demonstrate benefit in pediatric patients aged 12 to 17 years with symptomatic non-erosive GERD (sGERD). Study 207 provides the clinical efficacy and safety data to demonstrate benefit in pediatric patients aged 12 to 17 years for healing of erosive esophagitis, maintenance of healed erosive esophagitis, and relief of heartburn. The design of each of these two studies will be discussed individually below. A review of the efficacy data will be provided in Section 6 of this document. A review of the safety data will be provided in Section 7 of this document.

5.3 Discussion of Individual Studies

5.3.1 Study 206:

The goal of this open label study is to assess the safety and effectiveness of dexlansoprazole 30mg administered daily for four weeks, for treatment of symptomatic non-erosive GERD in pediatric patients 12 to 17 years of age. The study was conducted from June 22, 2012 through January 21, 2014.

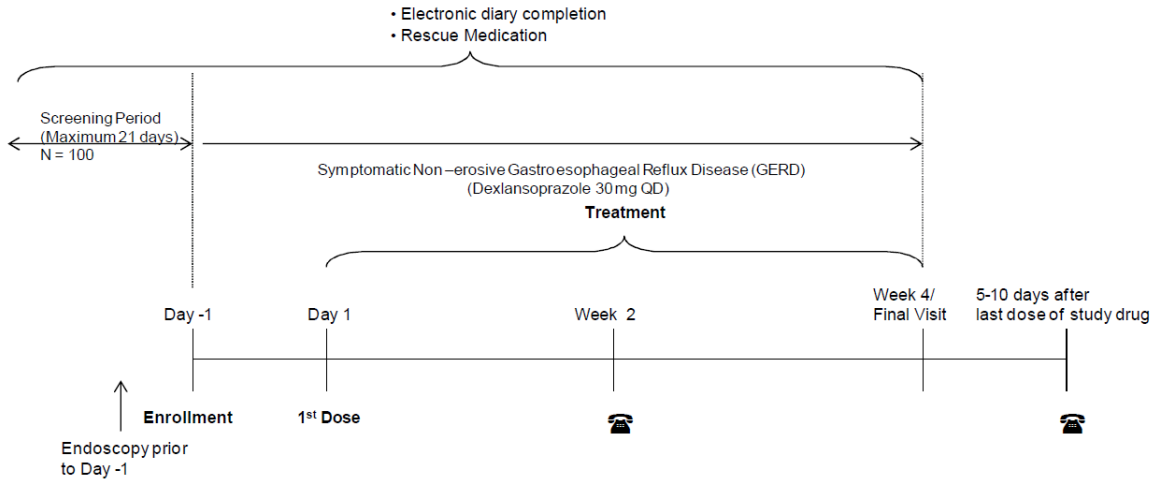
Title: "A Phase 2 Open-Label, Multicenter, 4-Week Study to Assess the Safety and Effectiveness of Daily Oral Administration of Dexlansoprazole Delayed-Release Capsules for Relief of Heartburn, in Adolescent Patients Ages 12 to 17 Years With Symptomatic Non-Erosive Gastroesophageal Reflux Disease."

Objectives: To assess the safety and effectiveness of treatment with once daily (QD) oral administration of dexlansoprazole delayed-release capsules (30mg) in adolescent patients aged 12 to 17 years with symptomatic non-erosive GERD.

Treatment: All patients received a QD dose of dexlansoprazole 30mg once daily without regard to food.

Design: The study was conducted as an open label, non-randomized study utilizing once daily treatment with dexlansoprazole in patients documented to have non-erosive, symptomatic GERD. The study included a screening period of up to 21 days, followed by the open label treatment which lasted 4 weeks, and a follow-up phone call conducted 5-10 days after the final study visit. All patients received the open label dose of 30mg daily dexlansoprazole. Figure 1 below shows the basic study design and points of evaluation.

Figure 1: Schematic of Study Design: TK206



(source: applicant's submission, sNDA 22287,TAKMR-390_206, protocol amendment 2, page 25/97)

Patient Population: Patients with a confirmed diagnosis of sGERD, 12 to 17 years of age were eligible for enrollment. Enrollment was contingent on patients having a documented baseline endoscopy that was negative for esophagitis, and frequency of patient-reported symptoms, based on eDiary entries, that met the inclusion criterion of symptoms on 3 of any 7 days. One hundred four patients were enrolled.

Study Procedures: All patients underwent a screening period of up to 21 days to determine initial eligibility. If patients qualified, based on presence of reflux symptoms on at least 3 of 7 consecutive days during the screening period (based on eDiary entries completed morning and night), they were then scheduled for further pre-enrollment testing. This included clinical examination, laboratory testing, and an upper endoscopy with biopsies, to document the diagnosis of non-erosive GERD and exclude other diseases of the esophagus. Patients were enrolled once all inclusion criteria were met. See Table 29 in Appendix for detailed schedule of study procedures.

In addition to the daily eDiary entries, patients also completed a patient reported outcome measure, the Pediatric Gastroesophageal Symptom and Quality of Life Questionnaire, short form [PGSQ-A-SF] (see Appendix, Figure 7) on the last day of the screening period (Day -1), and again at week 4 or early termination visit. Medication was dispensed, and they began taking the once daily dose of study medication the following day (study day 1).

Sites provided all patients with age appropriate rescue medication, dosed per product label. The rescue medications included magnesium hydroxide, or aluminum hydroxide, and could be combined with simethicone. Rescue medication use was permitted for relief of heartburn, acid indigestion, sour stomach, upset stomach, pressure or bloating.

During the study period (Day 1 to 28-35), patients documented the presence or absence of reflux symptoms, the degree to which symptoms hurt, and any use of rescue medications in an electronic diary (eDiary). Patients were instructed to make a diary entry each morning (to account for symptoms that occurred overnight) and each evening before bed (to account for symptoms from that day). See Appendix, Figure 8 for eDiary instructions and questions.

A telephone call was conducted at week 2, which included screening for adverse events, collection of information on concomitant medication use, and review of eDiary compliance. A follow-up clinic visit occurred at week 4/termination.

Inclusion Criteria
Patients were included in the study if the following criteria were met:

1. In the opinion of the investigator, the patient and parent(s) or legal guardian are capable of understanding and complying with protocol requirements.

2. Prior to any study-specific procedures being performed, the informed consent and the assent form, according to local country requirements, must be signed and dated by parent(s) or legal guardian and by the patient, respectively.

3. The patient has a medical history of symptoms of GERD for at least 3 months prior to screening, as assessed by the investigator.

4. The patient has met the electronic diary qualification criteria as assessed by the electronic daily diary defined as follows: heartburn (burning or hurting in your throat, chest, or stomach) on at least 3 of any 7 consecutive days.

5. The patient has non-erosive GERD with no evidence of definite endoscopic esophageal mucosal breaks as described in the Los Angeles Classification of Esophagitis at the screening endoscopy (see Appendix, Table 28).

6. The patient is male or female and aged 12 to 17 years, inclusive.

7. A male patient who is non-sterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception from signing of informed consent and assent throughout the duration of the study and for 30 days after last dose of study medication.

8. A female patient of childbearing potential who is or may become sexually active agrees to routinely use adequate contraception from the time of signing the informed consent and assent until 30 days after the last dose of study medication.

Exclusion Criteria:
Patients were excluded if any of the following criteria were met:

1. The patient has evidence of cardiovascular, pulmonary, central nervous system, hepatic, hematopoietic, renal, or metabolic, endocrine or gastrointestinal disease, or serious allergy, asthma, or allergic skin rash that suggests clinically significant, uncontrolled underlying disease or condition (other than the disease being studied), which may impact the ability of the patient to participate or potentially confound the study results.
2. The patient has a co-existing disease affecting the esophagus, (eg, esophageal varices, scleroderma, viral or fungal infection, or esophageal stricture), history of radiation therapy or cryotherapy to the esophagus, caustic or physiochemical trauma such as sclerotherapy to the esophagus.
3. The patient has a known history of Barrett's esophagus with dysplastic changes in the esophagus.
4. The patient has a known history of eosinophilic esophagitis (EoE) or endoscopic findings suggestive of EoE.
5. The patient has a history of celiac disease or the patient tests positive for tissue transglutaminase antibody (tTG) antibody.
6. The patient has active gastric or duodenal ulcers within 4 weeks prior to Day -1.
7. The patient has any finding in his/her medical history, physical examination, or safety clinical laboratory tests giving reasonable suspicion of underlying disease that might interfere with the conduct of the study.
8. Patient has taken any PPI within 1 week (7 days) prior to the Screening Visit.
9. The patient has a history of hypersensitivity or allergies to dexlansoprazole or any component of dexlansoprazole or any PPI, or any of the allowed rescue medications (including antacid containing Mg(OH)2 and / or Al(OH)3 or simethicone).
10. The patient is required to take excluded medications or it is anticipated that the patient will require treatment with at least one of the disallowed concomitant medications during the study evaluation period (See Appendix, Table 26 for full listing of excluded medications).
11. The patient has a history of malignant disease (except basal cell carcinoma) within 5 years prior to screening.
12. The patient has a condition that may require inpatient surgery during the course of the study.
13. The patient requires dilatation of esophageal strictures and/or has strictures preventing passage of the endoscope during the screening endoscopy. Schatzki's ring (a ring of mucosal tissue near the lower esophageal sphincter) is acceptable.
14. The patient is known to be positive for human immunodeficiency virus (HIV).
15. The patient has current or clinical history of Zollinger-Ellison syndrome or other hypersecretory condition.
16. The patient has a history of gastric, duodenal or esophageal surgery except simple oversew of an ulcer. A history of gastric tube and/or percutaneous endoscopic gastrostomy (PEG) placement is allowed.

17. The patient had an acute upper gastrointestinal hemorrhage within 4 weeks prior to endoscopy.
18. The patient has donated or lost ≥300 mL blood volume, undergone plasmapheresis, or has had a transfusion of any blood product within 90 days prior to the first dose of study drug.
19. The patient has a known history of alcohol abuse or illegal drug use within the past 12 months prior to the first dose of study drug.
20. The patient has any Screening Visit 1 abnormal laboratory value that suggests a clinically significant underlying disease or condition that may prevent the patient from entering the study; or the patient has: creatinine >1.5 mg/dL, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2 times the upper limit of normal (×ULN), or total bilirubin >2.0 mg/dL with AST/ALT elevated above the limits of normal values.
21. If female, the patient is pregnant or lactating or intending to become pregnant before, during or within 30 days after last dose of study medication; or intending to donate ova during such time period.
22. If male, the patient intends to donate sperm during the course of this study or within 30 days after last dose of study drug.
23. The patient, patient's Parent(s) or Legal Guardian is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study or may consent and assent under duress. Students of the institution/research facility who are under the supervision of, or in a subordinate role to, the investigator are also ineligible.
24. The patient or patient's Parent(s) or Legal Guardian, in the opinion of the investigator, is unlikely to comply with the protocol requirements or is unsuitable for any other reason.
25. The patient has participated in another clinical study and/or has received any investigational compound within 30 days prior to Screening.

Key outcomes measured:

Primary Endpoint:
The primary endpoint of the study was a safety endpoint defined as treatment emergent adverse events (TEAEs) experienced by ≥5% of patients while receiving dexlansoprazole during the treatment period.

Secondary Endpoint:
The secondary endpoint of the study was an efficacy endpoint: the percentage of days with neither daytime nor nighttime heartburn reported over the treatment period, as assessed by the electronic diary.

The percentage of days with neither daytime nor nighttime heartburn reported over the treatment period was calculated as:

$$\text{\% of days with neither daytime nor nighttime heartburn} = \frac{\text{(\# of heartburn-free days* during Treatment Period)}}{\text{(total \# of days with daytime or nighttime heartburn result marked during Treatment Period)}} \times 100\%$$

Days with missing entry for both daytime and nighttime were excluded from the numerator and denominator. The treatment period started on the first dose day and ended on the last dose day, or day 35, whichever came first. If the patient terminated prematurely, the treatment period was defined as first dose date to last dose date +1.

Exploratory Efficacy Endpoints:

- Percentage of days without nighttime heartburn over the 4 weeks, as measured by the eDiary
- Percentage of days without daytime heartburn over the 4 weeks, as measured by the eDiary
- Mean degree to which daytime and nighttime heartburn hurt over the 4 weeks (eDiary)[3]
- Severity of GERD symptoms per investigator assessment at week 4[4]
- Changes from baseline to week 4 in the Pediatric Gastroenterology Symptom Questionnaire, Adolescent, Short Form (PGSQ-A-SF) (patient reported)[5]
- Percentage of days without rescue medication use during the 4 weeks

Safety Monitoring:
In addition to the primary endpoint (TEAEs), the applicant also collected additional data to assess safety including changes in clinical laboratory test parameters, vital signs, and ECGs. All patients underwent a history and physical examination including measurement of vital signs at the screening visit and final study visit. Laboratory data including hepatitis panel, celiac antibody testing, ECG, CYP2C19 genotype, urine analysis and urine pregnancy test (females) were obtained at baseline and in follow-up per study schedule (Refer to Appendix, Table 30 for full schedule). Hematology, chemistry and urine tests were done at a central lab, and results were evaluated based on lab specified age appropriate normal ranges.

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3 Degree to which symptoms hurt was recorded by patients with their daily eDiary entries. Patients could report one of three answers: 1) did not hurt much, 2) hurt some, 3) hurt a lot. Subsequently, the mean degree to which heartburn hurt was derived by: 1. Taking the average degree to which daytime and nighttime heartburn hurt within a day, 2. Taking the mean average of the average daily degree to which daytime and heartburn hurt over the appropriate study days (including any days with at least one entry).
4 Investigators rated GERD symptom severity as "none, mild, moderate, severe, or very severe." Refer to Appendix, Table 27*.*
5 PGSQ-A-SF is a shortened version of the Pediatric Gastroenterology Symptom Questionnaire. The PGSQ contains 35 items, the shortened version utilized in this study contains 11 elements pertaining to GERD symptoms as well as their impact on quality of life. See Appendix, Figure 7 *for further details.*

Specific follow-up plans were in place for abnormal liver enzymes and magnesium. Any measured serum magnesium <1.1mEq/L would be verified by collection of a 24hr urine for magnesium excretion. Any patient who developed AST or ALT >3x the upper limit of normal would have follow-up liver function tests done within 7 days (goal of 48-72 hours later). If the abnormality persisted on the second measurement, additional investigation was performed and the result was recorded as an AE.

Changes in other laboratory test values were considered an AE only if they were judged by the investigator to be clinically significant.

Adverse events were coded using MedDRA terms. A Treatment Emergent Adverse Event (TEAE) was defined as any AE that started or worsened after study day 1, and no more than 30 days from last dose. TEAEs were summarized by severity and relation to study drug in the safety analysis. Severity was assessed by the investigator as either mild (easily tolerated by patient), moderate (caused discomfort and affected usual activities), or severe (caused considerable interference with usual activities).

Planned Method of Analysis:
There was no formal sample size calculation performed for this study. Results were described descriptively. Continuous data was summarized using number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data was summarized using the number and percentage of patient for each category where appropriate.
In the safety analysis, using a sample size of 100 patients, an incidence rate of 2% or 5% for a given AE, the probability of observing the event in at least one patient during the study was estimated at 87 or 99%, respectively.

Analysis Sets:
The safety analysis dataset set included all patients who received at least one dose of the study drug. The efficacy analysis set included all patients who received at least one dose of study drug and had post-baseline data. Both safety and efficacy datasets contained all 104 enrolled patients' data.

Subgroup Analysis:
Subgroup analysis was performed only by sex. Due to the restricted age group of enrollment (already limited to 12 – 17 years), racially homogenous population, and limited ethnicity data collected, no additional subgroup analyses were performed.

5.3.2 Study 207

The goal of this study was to assess safety and effectiveness of 60mg daily dexlansoprazole given for 8 weeks, to heal erosive esophagitis (EE) in pediatric patients 12 to 17 years of age, and then to determine safety and efficacy of continued treatment

with 30mg daily dexlansoprazole for an additional 4 months, for the maintenance of healing and control of heartburn.

Title: “A Phase 2, Multicenter, 36-Week Study to Assess the Safety and Effectiveness of Daily Oral Administration of Dexlansoprazole Delayed Release Capsules for Healing of Erosive Esophagitis and Maintenance of Healed Erosive Esophagitis and Relief of Heartburn in Adolescent Subjects Aged 12 to 17 Years”

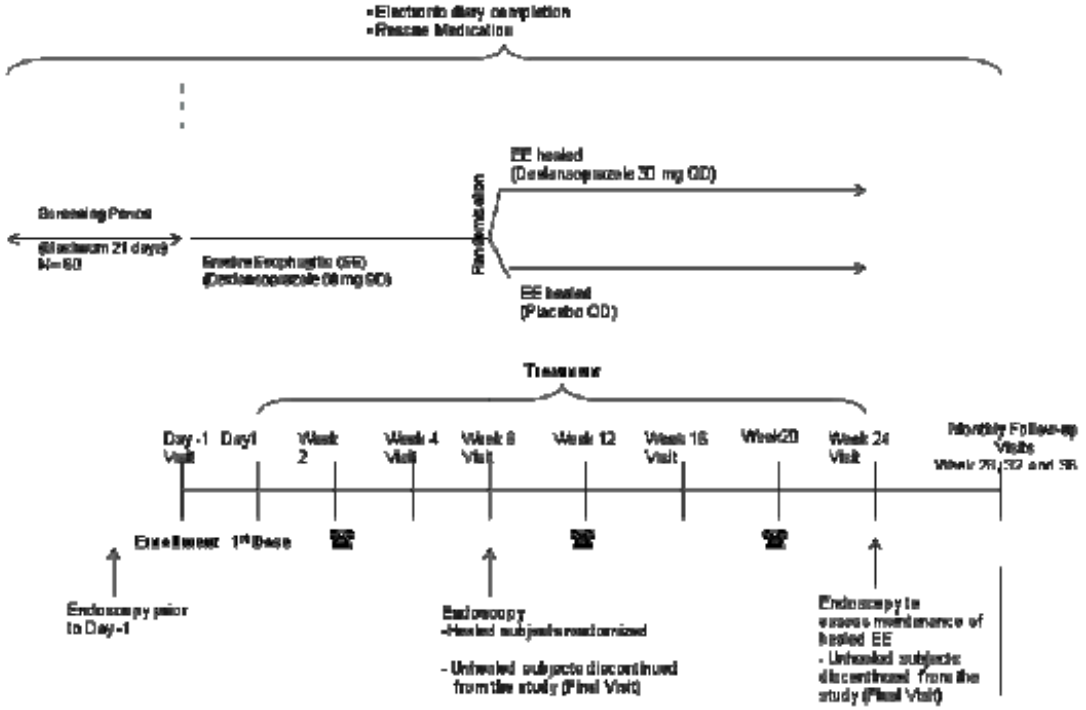
Objectives:
To assess the safety and effectiveness of 60mg daily oral administration of dexlansoprazole (given for 8 weeks) for the treatment of EE in adolescent patients aged 12 to 17 years, inclusive.

To assess the safety and effectiveness of 30mg daily oral administration of dexlansoprazole compared with placebo (given for 16 weeks), for the maintenance of healing in EE and relief of symptomatic heartburn in adolescent patients aged 12 to 17 years, inclusive.

Treatment and Duration: In the first phase of the study, all patients received dexlansoprazole 60mg daily orally for 8 weeks. In the second phase of the study, patients were randomized to receive either dexlansoprazole 30mg daily orally or placebo for an additional 16 weeks.

Study Design: This study was a phase 2, multicenter, multinational study in adolescents aged 12 to 17 years. The initial phase was an open-label study of 60mg daily dexlansoprazole for the healing of endoscopically documented erosive esophagitis. The second phase was a double-blind, placebo-controlled study of 30mg QD vs placebo for the maintenance of healing of EE, and control of symptoms of GERD in patients with healed EE. The study design is shown below in Figure 2.

Figure 2: Schematic of Study Design, TK 207



(source: applicant's sNDA22287 submission, Figure 9.a, clinical study report for study TAK-390MR_207, page 23)

Study Procedures:

Screening:
Patients were required to have a documented medical history of GERD symptoms for a minimum of 3 months prior to screening, and must have discontinued any prior PPI at least 7 days prior to screening. The screening phase was up to 21 days prior to enrollment during which patients completed the eDiary to document the presence and severity of any symptoms twice daily. Patients who experienced symptoms of heartburn on at least 3 of any 7 consecutive days were eligible to enroll. After meeting eDiary criteria, patients then underwent an endoscopy during the screening period, or within 1 week of signing informed consent, to determine if erosive esophagitis was present. Esophagitis was graded on the Los Angeles grading scale, grade A through D, where grade A represents small erosion(s) <5mm and not crossing 2 mucosal folds, and D involves severe erosion(s) extending across 75% of circumference (refer to Appendix, Table 28 for details of grading scale). If endoscopy was done within 7 days of enrollment demonstrating EE, heartburn symptoms based on diary were not required to qualify. Regardless, all subjects recorded symptoms twice daily in the eDiary, throughout the screening, treatment, and follow-up periods. During the screening period, and throughout the study, site provided rescue medication was allowed for use to treat breakthrough reflux symptoms. Provided rescue medication was an age

appropriate antacid ($Mg(OH)_2$ or $Al(OH)_3$) which could contain simethicone for relief of gas. Patients were instructed that rescue medication could be used for relief of acid indigestion, heartburn, sour stomach, upset stomach, pressure or bloating.

Treatment:
Study drug was dispensed on day -1, and patients began taking medication the following day (study day 1). During the 8 week treatment period, patients self-administered dexlansoprazole 60 mg daily in the morning without regard to food. At the week 8 visit, a repeat endoscopy was performed to determine whether healing of EE had occurred. If endoscopy confirmed EE was healed, patients were then randomized into the second phase of the study. Patients who were not healed had their final study visit, and were discontinued from further participation. There was no additional follow up described for patients who were not healed and discontinued from the study.

For the second phase of the study, patients with documented healing were randomized to receive either 30mg of dexlansoprazole QD or placebo for an additional 16 weeks. A repeat endoscopy was performed at week 24, to determine if healing was maintained, or if there was evidence of recurrence of EE. Throughout the entire study, patients documented their symptoms in the eDiary twice daily. Control of heartburn symptoms, as well as need for rescue medication use was continually assessed throughout the trial by eDiary entries. Additional exploratory efficacy measures were also collected, including physician reported GERD symptom assessment, and Pediatric Gastroenterology Symptom Questionnaires (PGSQ-A-SF) that were completed at study visits.

Follow-up:
At week 24, patients with relapsed EE were discontinued from the study and this was considered the final study visit. Patients who maintained healing were then instructed to discontinue study drug, and entered a 3 month follow-up period, where they were followed with monthly clinic visits, and continued to document symptoms in the eDiary, to determine if symptoms recurred, and to obtain additional safety monitoring data. These patients were followed for a full 3 months, or until symptoms returned which required an invasive procedure or treatment with a PPI or histamine-2-receptor antagonist (H2RA). A comprehensive table demonstrating the timing of all required visits and assessments is included in the Appendix, Table 29.

Inclusion criteria:
Patients were enrolled in the study if the following criteria were met:

1. In the opinion of the investigator, the patient and parent(s) or legal guardian were capable of understanding and complying with protocol requirements.
2. Prior to any study-specific procedures being performed, the informed consent and the assent form, according to local country requirements, was signed and dated by parent(s) or legal guardian and by the patient.

3. The patient had a medical history of symptoms of GERD for at least 3 months prior to screening.
4. The patient met the eDiary qualification criteria for heartburn (burning or hurting in your throat, chest, or stomach) present on at least 3 of any 7 days.
5. The patient had endoscopic evidence of EE (LA Grade A-D) based on the screening endoscopy performed either during the Screening Period or within 1 week prior to signing informed consent and assent.
6. The patient was aged 12 to 17 years, inclusive.
7. A male patient who was non-sterilized and sexually active with a female partner of childbearing potential agreed to use adequate contraception from signing of informed consent and assent throughout the duration of the study and for 30 days after last dose of study medication.
8. A female patient of childbearing potential who was or may have become sexually active agreed to routinely use adequate contraception from the time of signing the informed consent and assent until 30 days after the last dose of study medication.

Exclusion criteria:
Patients were excluded from the study if any of the following criteria were met:

1. The patient had evidence of cardiovascular, pulmonary, central nervous system, hepatic, hematopoietic, renal, metabolic, endocrine or gastrointestinal disease, or serious allergy, asthma, or allergic skin rash that suggests clinically significant, uncontrolled underlying disease or condition (other than the disease being studied), which may have impacted the ability of the subject to participate or potentially confounded the study results.
2. The patient had a co-existing disease affecting the esophagus (eg, esophageal varices, scleroderma, viral or fungal infection, or esophageal stricture), history of radiation therapy or cryotherapy to the esophagus, caustic or physiochemical trauma such as sclerotherapy to the esophagus.
3. The patient had known history of Barrett's esophagus, with dysplastic changes in the esophagus.
4. The patient had a known history of eosinophilic esophagitis (EoE) or endoscopic findings suggestive of EoE.
5. The patient had a history of celiac disease or patient tested positive for tissue transglutaminase (tTG) antibody.
6. The patient had active gastric or duodenal ulcers within 4 weeks prior to Day -1.
7. The patient had any finding in his/her medical history, physical examination, or safety clinical laboratory tests that gave reasonable suspicion of underlying disease that might have interfered with the conduct of the trial.
8. The patient had taken any PPI within 1 week (7 days) prior to the Screening Visit.
9. The patient tested positive for *H. pylori*.
10. The patient had a history of hypersensitivity or allergies to dexlansoprazole or any component of dexlansoprazole or any PPI (including lansoprazole,

omeprazole, rabeprazole, pantoprazole, or esomeprazole) or antacid containing Mg(OH)2 and/or Al(OH)3 or simethicone.

11. The patient was required to take excluded medications or it was anticipated that the patient would require treatment with at least 1 of the disallowed concomitant medications during the study evaluation period as specified in the Excluded Medications and Treatments (see Appendix, Table 26).
12. The patient had a history of malignant disease (except basal cell carcinoma) within 5 years prior to screening.
13. The patient had a condition that may have required inpatient surgery during the course of the study.
14. The patient required dilatation of esophageal strictures and/or had strictures preventing passage of the endoscope during the screening endoscopy. Schatzki's ring (a ring of mucosal tissue near the lower esophageal sphincter) was acceptable.
15. The patient was known to be human immunodeficiency virus (HIV) positive.
16. The patient had current or clinical history of Zollinger-Ellison syndrome or other hypersecretory condition.
17. The patient had a history of gastric, duodenal, or esophageal surgery except simple oversew of an ulcer. A history of gastric tube and/or percutaneous endoscopic gastrostomy (PEG) placement was allowed.
18. The patient had an acute upper gastrointestinal hemorrhage within 4 weeks prior to endoscopy.
19. The patient had donated or lost ≥300 mL blood volume, underwent plasmapheresis, or had a transfusion of any blood product within 90 days prior to the first dose of study drug.
20. The patient had a known history of alcohol abuse or illegal drug use within the past 12 months prior to the first dose of study drug.
21. The patient had any Screening Visit 1 abnormal laboratory value that suggested a clinically significant underlying disease or condition that may have prevented the patient from entering the study; or the patient had: creatinine >1.5 mg/dL, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2 times the upper limit of normal (×ULN), or total bilirubin >2.0 mg/dL with AST/ALT elevated above the limits of normal values.
22. If female, the patient was pregnant or lactating or intended to become pregnant before, during, or within 30 days after last dose of study medication; or intended to donate ova during such time period.
23. If male, the patient intended to donate sperm during the course of this study or within 30 days after last dose of study drug.
24. The patient, patient's parent(s) or legal guardian was an immediate family member, study site employee, or was in a dependent relationship with a study site employee who was involved in the conduct of this study or may have consented and assented under duress. Students of the institution/research facility who were under the supervision of, or in a subordinate role to, the investigator were also ineligible.

25. The patient or patient's parent(s) or legal guardian, in the opinion of the investigator, was unlikely to comply with the protocol requirements or was unsuitable for any other reason.
26. The patient participated in another clinical study and/or received any investigational compound within 30 days prior to screening.

Key outcomes measured:

Safety and efficacy endpoints will be discussed below. Safety endpoints include adverse event listings and laboratory and vital sign changes. Efficacy endpoints will be discussed according to indication including 1) healing of EE by week 8, 2) maintenance of healing at week 24, and 3) control of heartburn symptoms.

Safety Endpoints:
The primary endpoints for safety were:

1. Treatment emergent adverse events (TEAEs) experienced by ≥5% of patients during the 8 week study period for healing of EE.
2. TEAEs experienced by ≥5% of patients during the 16 week study period for the maintenance of healed EE.

Additional Safety Measures:
Information on clinical laboratory test results, ECG, vital signs, and changes on physical examination were also collected. See Appendix, Table 30, for full listing of clinical laboratory tests. Severity of adverse events was assessed by the investigator as described above in section 5.3.1.

Efficacy Endpoints:
Efficacy assessments are described below by proposed indication.

Healing of EE:
The main efficacy endpoint to support a claim for healing of EE was the percentage of patients with healed EE at 8 weeks, per endoscopy.
This was calculated as the number of patients with healing at 8 weeks, divided by the number of patients that had post-baseline data and endoscopy results at week 8.

Enrolled patients underwent endoscopy at the week 8 visit, and the appearance of the esophagus was graded according to LA Grade. Only those patients who demonstrated healed EE were eligible to continue to the second phase of the trial.

Although the applicant used the pre-specified full analysis set to calculate the efficacy endpoint, in the opinion of this reviewer, the method that the applicant used to calculate the percentage of patients with healed EE at week 8 is not based on an intention to treat calculation (e.g., percentage of patients healed at week 8, calculated as the number of patients healed at week 8, divided by the total number of patients enrolled at the start of

the study). However, this method does account for per-protocol analysis. Importantly, the method used by the applicant was pre-specified in the statistical analysis plan, and is analogous to the calculations performed to determine the percentage of patients healed in the adult trials. Therefore, using the same method to determine the efficacy endpoints further facilitates extrapolation of efficacy from the larger adult trials. Refer to statistical review by Dr. Andrejus Parfionovas (primary reviewer) and Dr. Yeh-Fong Chen (secondary reviewer) for further details.

Maintenance of Healing:
The percentage of patients who maintained healing of EE from week 8 to week 24, based on endoscopy, was the main efficacy endpoint to support approval and labeling of the maintenance of healed EE.

This percentage of patients who maintained healing of EE from week 8 to week 24 was calculated as the number of patients who had a normal appearing esophagus at week 24, divided by the number of patients who had endoscopy results at week 24. Results were presented by treatment group.

Patients with documented healing at week 8 who completed treatment through week 24 underwent repeat endoscopy at the week 24 visit, and the appearance of the esophagus was assessed based on LA Grade. Patients who maintained healing went on to the follow-up period where they were followed for an additional 12-weeks without treatment.

This reviewer again notes that this is not strictly an intention-to-treat analysis of maintenance of healing. However, the method used by the applicant to calculate the percentage of patients who maintained healing of EE was pre-specified in the statistical analysis plan, and is analogous to the calculations used in the adult trials, supporting extrapolation. Refer to statistical review by Dr. Andrejus Parfionovas (primary reviewer) and Dr. Yeh-Fong Chen (secondary reviewer) for further details.

Symptom Control:
The percentage of days with no heartburn symptoms recorded (day or night) based on eDiary entries was the main efficacy endpoint to support approval and labeling for the control of heartburn symptoms in patients with EE.

Symptom control was assessed throughout the trial, including:

- The first 8 weeks of treatment (dexlansoprazole 60 mg capsule)
- The maintenance phase of treatment (weeks 8 to 24) (dexlansoprazole 30 mg capsule vs placebo)
- The follow-up period (week 24 onward, off treatment) to assess persistence of therapeutic effect/time to recurrence once treatment was discontinued.

Patients documented the presence of heartburn (i.e., yes/no) in the morning and evening, as well as the degree to which heartburn hurt (i.e., did not hurt very much, hurt some, or hurt a lot). See Appendix, Figure 8, for the diary questions used.

The diary was designed to allow patients to report symptoms using an age-appropriate tool, with the expectation that adolescents can report "heartburn" similarly to adults. The same eDiary tool was used to collect symptom data in both study 206 and study 207.

The outcome measure was calculated as follows:

$$\text{\% of days with neither daytime nor nighttime heartburn} = \frac{\text{(\# of heartburn-free days* during Treatment Period)}}{\text{(total \# of days with daytime or nighttime heartburn result marked during Treatment Period)}} \times 100\%$$

* All entries on a day must have been heartburn-free in order for the day to be counted as a day with neither daytime nor nighttime heartburn.

Days with missing results for both morning and nighttime entry were excluded from both numerator and denominator.

Exploratory Outcomes:

Data for a number of other exploratory outcome measures (both patient reported and investigator scored) were also collected for each phase of the study, including:

First 8 weeks:

- Percentage of days without nighttime heartburn over the first 8 weeks (eDiary)
- Mean degree to which daytime and nighttime heartburn hurt during the first 8 weeks (eDiary)
- Investigator determined severity of GERD symptoms, assessed at week 4 and week 8
- Change from baseline to week 4 and week 8 in the total and subscale scores for PGSQ-A-SF

Week 8 to 24 (patients with documented healing at 8 weeks):

- Percentage of days without nighttime heartburn over weeks 8 to 24 (eDiary)
- Mean degree to which daytime and nighttime heartburn hurt over weeks 8 to 24 (eDiary)
- Investigator determined severity of GER symptoms at week 16 and week 24
- Change from week 8 to week 24 in the total and subscale scores for the PGSQ-A-SF

In general, the exploratory endpoints provide several different means to assess heartburn symptoms. In the opinion of this reviewer, the eDiary is the most direct measure, and least subject to bias since the report is obtained from the patient. Therefore, this reviewer agrees with the applicant's efficacy assessment that the changes based on the eDiary reports should be the main focus of the efficacy outcomes. While it may be informative to also evaluate changes based on the Investigator-scored or other questionnaire-based tools, these other methods of assessing heartburn are subject to bias. Specifically, the Investigator-based tool requires another person to interpret the severity of what the patient is experiencing or feeling, rather than an assessment of signs and symptoms that are observable to the investigator. Unlike infants and very young pediatric patients, patients who are at least 12 years of age are expected to be able to self-report. Additionally the Questionnaire-based tool requires patients to recall symptoms over a 7 day period, potentially introducing recall bias.

Analysis Datasets:
The safety analysis data was separated into 2 datasets, one for the open-label 8 week portion of the study (healing of EE) and one for the double-blind 16 week portion of the study (maintenance of healing of EE). The safety analysis dataset for the open-label portion (Safety Analysis OL) includes all patients enrolled at the start of the study who received at least one dose of study drug. The safety analysis data set for the double blind portion of the study (Safety Analysis DB) includes all patients with documented healing at week 8, who continued into the second phase of the study, and received at least one dose of study drug after the week 8 visit.

The full analysis set was also defined separately for the open label and double blind portions of the study. The full analysis set for the first 8 weeks (Full Analysis OL) included all patients who received at least one dose of study drug, and who had post-baseline data for the efficacy variable (in this case endoscopy results at week 8). The full analysis set for the subsequent 16 weeks (Full Analysis DB) included patients with healed EE at week 8, who received at least one dose of study drug in the maintenance phase and had post-baseline data available from week 8 to 24 for efficacy variables (including endoscopy result at week 24).

Statistical Analysis:
A formal sample size calculation was not conducted. For the purposes of adverse event detection, it was estimated that with a sample size of 60 patients, and an anticipated dropout rate of 33%, an adverse event with an incidence of 5% would be detected in 95% of cases.

Efficacy Analysis:
Efficacy was assessed using the full analysis data sets. The crude healing rate of EE at week 8 is defined as the percentage of patients who have healing at week 8 (out of all those who underwent endoscopy) with a 95% confidence interval.

For efficacy measures at week 24, the percentage of patients with maintained healing at the week 24 endoscopy were compared between treatment groups using Fisher's exact test. If a final endoscopy was performed prior to week 24 and indicates recurrence of EE, this patient was included as "recurrence at week 24."

Percentage of days without heartburn and mean degree to which heartburn hurt were calculated using the same methods as described above for study 206. Changes in PGSQ-A-SF were summarized descriptively.

Safety Analysis:
Treatment emergent adverse events (TEAE) were defined as any AE that started or worsened after study day 1, and no more than 30 days after the last dose of the study drug. TEAEs occurring during the first 8 weeks were listed in Safety Analysis Set –OL. TEAEs for patients who entered the double blind period, if the event occurred during the 16 week double blind period, or within 30 days of the last dose, were included in the Safety analysis set -DB. For those who entered the follow-up period, AEs occurring after the last dose, but within the 12 week follow-up period were summarized by DB treatment group.

6 Review of Efficacy

Efficacy Summary

This efficacy supplement contains data from 2 clinical studies (study 206 and study 207) conducted to assess the safety and effectiveness of dexlansoprazole in pediatric patients 12 to 17 years of age for the following indications:

a. Treatment of heartburn associated with symptomatic non-erosive GERD
b. Healing of all grades of erosive esophagitis (EE)
c. To maintain healing of EE and relief of heartburn

Study 206 was a four week, open label study to evaluate the effect of dexlansoprazole 30 mg daily for the treatment of heartburn in 104 patients 12 to 17 years of age with symptomatic non-erosive GERD (sGERD). The primary outcome was safety, measured as treatment emergent adverse events (TEAEs) seen in ≥5% of patients. The secondary outcome (main efficacy outcome) was the percentage of 24 hour periods without daytime or nighttime heartburn. The pathophysiology of sGERD is sufficiently similar between adults and pediatric patients 12 to 17 years of age, as is the disease progression and response to intervention, which supports partial extrapolation of efficacy. 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, there was no additional clinical benefit with doses higher than 30 mg for the treatment of sGERD. Therefore, while an open-label, single arm trial is not the ideal trial design, the dose selected for this pediatric trial appears

reasonable. The efficacy data from this open label trial demonstrated similar rates of symptom control as seen in the larger, controlled clinical trials that supported product labeling in adults. During 8 weeks of treatment, the median percentage of days with neither daytime or nighttime heartburn reported was 47% (compared with 55% in the adult trials[6]). The use of dexlansoprazole in this age group for the treatment of sGERD is supported by evidence from adequate and well-controlled studies of Dexilant capsules in adults, and by safety and pharmacokinetic studies performed in pediatric patients.

Study 207 was a 36 week trial to assess the safety and efficacy of dexlansoprazole 60 mg on healing of EE, and dexlansoprazole 30 mg or placebo for the maintenance of healing of EE, and control of heartburn symptoms, in pediatric patients 12 to 17 years of age. The pathophysiology and response to treatment for healing of EE in pediatric patients 12 to 17 years of age is sufficiently similar to that of adults to facilitate partial extrapolation. Due to uncertainties regarding the need for maintenance therapy in this population, the maintenance portion of the study was a randomized withdrawal design to better assess the need for ongoing treatment after healing.

The first phase was an open-label, single arm study in 62 patients 12 to 17 years of age with endoscopically proven EE to evaluate the healing of EE over 8 weeks of treatment with dexlansoprazole 60 mg. The primary outcome was safety, measured as TEAEs seen in ≥5% of patients. The secondary outcome (main efficacy endpoint) at week 8 was the crude rate of healing of EE. Healing was determined based on the gross endoscopic appearance of the mucosa. Of the 62 patients enrolled, 58 patients completed the 8 week treatment period. Fifty-one out of these 58 (88%) patients had documented healing of EE. Healed patients were then randomized to receive either dexlansoprazole 30 mg daily or placebo for an additional 16 weeks. The main efficacy endpoints for this portion of the study were 1) the crude rate of maintenance of healing of EE at week 24, and 2) the control of heartburn symptoms, measured as percentage of 24 hour periods with neither daytime nor nighttime heartburn symptoms reported, based on electronic diary (eDiary) entries.

Results from endoscopy performed at week 8 showed a rate of healing of 88%, analogous to what was demonstrated in the adult trials (85-87%). Results of endoscopy performed at week 24 demonstrated the rate of maintenance of healing to be 82% in the dexlansoprazole arm and 58% in the placebo arm, compared with data from the adult trials where maintenance of healing of EE on treatment was 66% and 14% in the placebo arm. It is important to note that 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, 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

6 Approved product label for Dexilant, updated 2/2/2016, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022287s020lbl.pdf

points and the decline over time suggests that the placebo rate in pediatric patients may have also declined by 6 months. 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, for patients who maintained healing from week 8 to week 24, the difference between treatment and placebo was most notable in those with Grade B esophagitis (9/11 [82%] on treatment vs 1/8 [13%] on placebo). Despite the overall high placebo rate, the data suggest that there may be a subset of patients who require maintenance therapy, including patients with more severe disease.

This reviewer concludes that the data support the approval of dexlansoprazole for the healing of all grades of EE and to maintain healing of EE in pediatric patients 12 to 17 years of age. The rate of healing in the initial 8 weeks was analogous to that demonstrated in adult placebo controlled trials. The data from the maintenance phase demonstrate that in patients 12 to 17 years of age, a greater percentage maintained healing on treatment, compared with placebo. In the small subset of patients with more severe disease (Grade B vs. Grade A), the benefit of maintenance treatment was more pronounced compared to placebo.

Study 207 also evaluated the control of heartburn during healing and maintaining of healing of EE. Overall, patients reported improvement in symptoms over the course of the study. The baseline percentage of heartburn free 24 hours periods was approximately 14% during the screening period. Over the first 8 weeks of treatment, the median percentage of heartburn free 24 hour periods improved to 66%. During the maintenance phase, there was further improvement to 87% in patients who were randomized to receive treatment with dexlansoprazole, compared with 68% in the placebo group. Additional exploratory efficacy measures were assessed but did not demonstrate a clear difference in symptoms between treatment and placebo groups. Based on the eDiary entries, this reviewer concludes that treatment with dexlansoprazole 30 mg daily for an additional 4 months provides improved control of heartburn symptoms compared with placebo.

In the following sections of this document, the results of study 206 (treatment of symptomatic non-erosive GERD) will be reviewed first, followed by a review of the results from study 207.

6.1 Indication 1 – Treatment of symptomatic non-erosive GERD (sGERD)

Results of study 206 were submitted in support of the claim that dexlansoprazole delayed release capsules (30mg daily) are indicated in adolescents 12 years of age and older for the treatment of heartburn associated with sGERD.

In this study, the primary aim was to demonstrate safety in the adolescent population, and the secondary aim was to demonstrate effectiveness based on symptom diaries, which can be compared to similar measures used in the adult studies. The efficacy data is discussed below, with a detailed safety analysis in section 7.

6.1.1 Methods

Extrapolation of Efficacy:
The use of Dexilant in this age group for the treatment of symptomatic non-erosive GERD (sGERD) is supported by evidence from adequate and well-controlled studies of Dexilant capsules in adults, and by safety and pharmacokinetic studies performed in pediatric patients. Efficacy will be partially extrapolated from adequate and well-controlled trials conducted in adults to support the pediatric indication of treatment of sGERD. The pathophysiology of sGERD is sufficiently similar between adults and pediatric patients 12 to 17 years of age (i.e., adolescent patients), therefore, the disease progression and response to intervention is expected to be similar. Based on the results of pharmacokinetic (PK) studies, the exposure-response between adults and pediatric patients 12 to 17 years of age is similar. Refer to clinical pharmacology review by Dr. Shen Li for further details. As there were no pharmacodynamic data (e.g., intragastric pH) collected during the pediatric trials in this age group, 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 patient reported symptoms, collected by age-appropriate questionnaires, can be used to compare efficacy with similar measures used in the adult studies. 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, there was no additional clinical benefit with doses higher than 30 mg for the treatment of sGERD. Therefore, while an open-label, single arm trial is not the ideal trial design, the dose selected for this pediatric trial appears reasonable. In addition, dexlansoprazole is the sixth in class for PPIs, so there is an understanding of the mechanism of action, evidence from adequate and controlled trials across ages, indications, and products to support the efficacy of PPI therapy. For these reasons, efficacy will be extrapolated from adequate and well-controlled trials in adults.

Study 206 was conducted using similar methodology and outcomes to the adult trial, to facilitate extrapolation. Refer to section 5.3.1 above for detailed description of the study design.

6.1.2 Demographics

A total of 104 patients ages 12 to 17 years were enrolled into study 206; 102 patients completed treatment. All enrolled patients were included in the full analysis dataset. Two patients discontinued the study early and are discussed below in the safety

analysis (section 7). The mean age of enrolled patients was 15 ± 1.5 years. Patients were enrolled from 8 countries, including the United States, Hungary, Poland, Portugal, Mexico, Brazil, Italy and Belgium.

Table 5 below summarizes the key demographic features of the enrolled population.

Table 5: Demographic Data, study 206

	Dexilant 30mg (N=104)
Age (years)	
Mean ±SD	15 ± 22
Median (Range)	15 (12, 17)
12-14 years (%)	34 (33)
15-17 years (%)	70 (70)
Gender (n, %)	
Female	73 (70)
Race (n, %)	
Black or African American	6 (66)
White	95 (91)
Multiracial	3 (33)
Ethnicity (n, %)	
Not Hispanic of Latino	47 (45)
Hispanic or Latino	19 (18)
Not collected[1]	38 (37)
BMI kg/m^2	
Mean (SD)	23 (4)
Median	22
H. pylori status (n, %)	
Negative	90 (87%)

[1]*Ethnicity data was only collected at US sites*
(source: reviewer's table, created from data in applicant's sNDA22287 submission, received 9/30/15, clinical study report for study 206, end of text table 15.1.6.1).

The demographics of the studied population are notable for a preponderance of older patients (70% were 15-17 years of age), and white patients (91% white). Ethnicity data could not be adequately analyzed as data were not collected on ethnicity for patients enrolled outside the U.S., which accounts for 37% of the study population. Non-US patients enrolled from various nations including Hungary, Poland, Portugal, Mexico, Brazil, Italy, and Belgium, and represent patients of varying ethnicities. Despite the predominance of patients 15 to 17 years of age, it is unlikely that the pathophysiology of GERD would differ in patients 12-14 years vs 15-17 years of age. In this reviewer's opinion, the preponderance of older adolescents is unlikely to impact the efficacy results. The race distribution in this study is similar to the patient population included in

the adult studies used for approval, though a slightly higher proportion of Caucasian pediatric patients were enrolled. The approved product labelling for adults does not indicate any differences based on race or ethnicity, and this reviewer concludes that race and ethnicity are unlikely to be factors affecting efficacy for pediatric patients 12 to 17 years of age.

6.1.3 Patient Disposition

One hundred sixty-one patients were screened and 104 patients enrolled. Two patients discontinued the study drug prematurely due to adverse events (GERD and dizziness), and the remaining 102 patients completed the study.

6.1.4 Analysis of Primary Endpoint

The primary endpoint of this study was a safety outcome (TEAEs seen in ≥5% of patients) and is discussed in depth in section 7 below.

6.1.5 Analysis of Secondary Endpoint

The secondary endpoint of the study (i.e., primary efficacy endpoint) was "the percentage of days with neither daytime nor nighttime heartburn over the four weeks of treatment as assessed by eDiary."

The percentage of days with neither daytime or nighttime heartburn was calculated as follows[7]:

$$\text{\% of days with neither daytime nor nighttime heartburn} = \frac{\text{(\# of heartburn-free days* during Treatment Period)}}{\text{(total \# of days with daytime or nighttime heartburn result marked during Treatment Period)}} \times 100\%$$

This 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 to adolescent patients with sGERD. Given that patients recorded their symptoms twice daily, recall bias was minimized. Days with missing diary results for both daytime and nighttime were excluded from both the numerator and denominator, when calculating the efficacy endpoint, which is reasonable handling of the missing data, in the opinion of this reviewer. Study drug compliance was calculated as: (total count of capsules taken/total number of days on study drug) x100%. Mean study drug compliance was excellent, at 97%± 13%. Compliance with the electronic diary recording was calculated as (# of days

[7] In order for a day to count in numerator, a "heartburn free" entry must have been entered in both the AM and PM. The days with missing eDiary results for both daytime and nighttime were excluded from both the numerator and denominator.

with 2 eDiary entries collected during treatment period)/(# of days with 2 eDiary entries expected during the treatment period) x100%. Electronic diary compliance was reasonable at 83% ± 19%.

Results:
At baseline, the median percentage of days with neither daytime nor nighttime heartburn was 14% as compared to 47% during the treatment period. The observed increase in the heartburn free days from baseline demonstrates a meaningful improvement in symptoms for the pediatric patients in this study. These results are comparable to results in the adult trial which supported initial product labelling, where the median percentage of heartburn free days was 55% during treatment, compared with 19% in the placebo control group.[8] The efficacy of Dexilant for the control of sGERD is partially extrapolated from adequate and well controlled trials in adults, refer to section 6.1.1. above.

6.1.6 Analysis of Additional / Exploratory Endpoint(s):

The following additional endpoints were evaluated:

1. The percentage of days without nighttime heartburn over the 4 weeks of treatment as assessed by eDiary.
2. The percentage of days without daytime heartburn over the 4 weeks of treatment as assessed by eDiary.
3. The mean degree to which daytime and nighttime heartburn hurt during the 4 weeks of treatment as assessed by eDiary.
4. The severity of GERD symptoms at Week 4 as assessed by the investigator.
5. Changes from Baseline to Week 4 in the subscale scores on the Pediatric Gastroenterology Symptom Questionnaire, Adolescent, Short Form (PGSQ-A-SF).
6. Percentage of days without rescue medication use during treatment as assessed by eDiary.

Table 6 and Table 7 highlight these data, which are discussed in more detail below.

8 Approved product label for Dexilant, updated 2/2/2016, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022287s020lbl.pdf

Table 6: Comparison of Exploratory Outcome Measures, Screening vs Treatment

	Screening Mean ± SD	**Treatment Mean ± SD**
% of days without daytime heartburn Mean ±SD Median Range	 26 ± 26 14 (0, 100)	 55 ± 32 59 0,100
% of days without nighttime heartburn Mean ±SD Median Range	 44 ±33 43 (0,100)	 69 ± 31 81 0,100
Mean degree to which daytime and nighttime heartburn hurt [1]	1.19 ± 0.7	0.7 ± 0.6
Mean PGSQ-A-SF symptom subscale score[2]	2.5 ± 0.8	1.8 ± 0.8
Mean PGSQ-A-SF Impact subscale score	2.6 ± 1	1.9 ± 1

[1]Mean degree to which heartburn hurt was scored on scale of 0=none, 1=did not hurt very much, 2=hurt some, 3=hurt a lot
[2]Refer to Appendix, Figure 7: Patient Reported Outcome Tool (PGSQ-SF-A) for details.
(source: reviewer's analysis. Baseline data was provided by applicant in response to Information Request, received 6/10/2016, week four results from submitted dataset, Table 15.2.1, end of study report tables (page 104/362))

Since GERD is characterized by both daytime and nighttime symptoms and both daytime and nighttime symptoms are encompassed in the 24-hour period that is currently labeled for Dexilant, this reviewer does not recognize isolated daytime or nighttime heartburn as a unique entity of clinical importance.

There is a trend toward improvement in the "mean degree to which heartburn hurts" from baseline compared with treatment; however, the patients did not appear to have a large amount of discomfort at baseline, as defined by this tool, given that the baseline mean was 1.19, which equates to approximately 1 on the scoring system. A score of 1 means that it "did not hurt very much." Therefore, a small change after treatment to a score of 0.7 is unlikely to be clinically meaningful.

PGSQ-A-SF scores are based on two sets of questions – those which focus on how often symptoms occurred (scored as 1=0 days, 2= 1 or 2 days, 3 = 3 or 4 days, 4 = 5 or 6 days and 5 = every day) and those which focused on the impact of symptoms (scored

as 1=never, 2= almost never, 3 = sometimes, 4= almost always, and 5 = always). The mean PGSQ-A-SF subscale scores demonstrate a lower score in those on treatment, compared to their baseline status, however, again the changes are small (2.5 to 1.8 for symptoms, and 2.6 to 1.9 for impact). It is unclear how meaningful this small decrease would be. Furthermore, there are aspects of this instrument that make the results less reliable compared with direct daily reporting of symptoms, for example, the recall period of 7 days. Seven day recall may be difficult for a pediatric patient to accurately record symptoms as compared to a daily diary. This reviewer notes that these instruments have not been qualified by the FDA as assessment tools that are appropriate for the purposes of supporting labeling claims. These limitations make conclusions based on this data less rigorous, and so this reviewer concludes that it is most appropriate to focus on the primary efficacy outcome measure, based on patient reports from the eDiary daily entries.

The following data (Table 7) shows the changes in investigator determined severity of symptoms commonly associated with GERD.

Table 7: Changes in Investigator recorded GERD symptoms from baseline to week 4

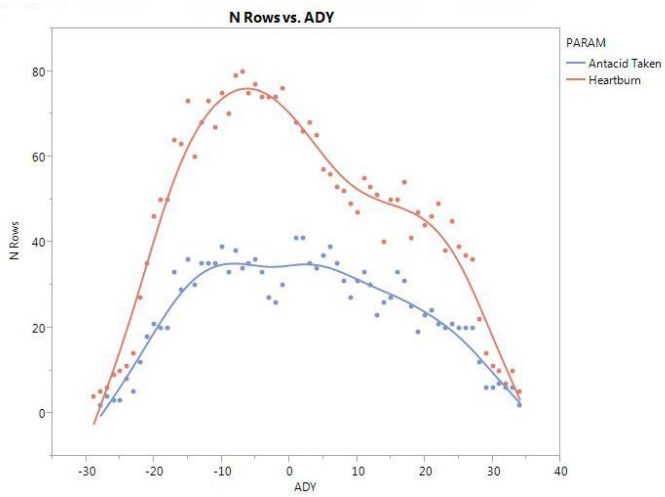
Intensity	Heartburn n (%[1])		Acid Regurgitation n (%)		Dysphagia n (%)		Belching n (%)		Epigastric Pain n (%)	
	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment
None	8 (8)	46 (48)	23 (22)	57 (60)	74 (71)	82 (86)	35 (34)	61 (64)	21 (20)	50 (53)
Mild	25 (24)	39 (41)	25 (24)	25 (26)	12 (12)	7 (7)	29 (28)	24 (25)	25 (24)	34 (36)
Moderate	46 (44)	8 (8)	34 (33)	11 (12)	9 (9)	4 (4)	22 (21)	5 (5)	33 (32)	7 (7)
Severe	21 (20)	2 (2)	18 (17)	2 (2)	6 (6)	2 (2)	13 (13)	4 (4)	21 (20)	4 (4)
Very Severe	1 (1)	0	1 (1)	0	0	0	2 (2)	1 (1)	1 (1)	0

[1] *percentages were calculated as n/# of patients with available data. (Baseline group had 101 with available data, treatment group had 95 with evaluable data at week 4)*
(source: reviewer's table, including data from applicant's provided Table 15.1.6.2 (Baseline GERD symptoms) and Table 15.2.4 (GERD symptoms Investigator Assessment)in End of Text Tables and Figures, clinical study report for study 206, pg 119)

This measure required investigators to ask patients to recall their experiences, and then for the investigator to interpret those results. In the opinion of this reviewer, this introduces additional bias (including patient recall bias, as well as investigator bias) since the investigator is reporting and interpreting on what the patient experiences. However, it is noted that the percentage of patients reporting "none" to "mild" intensity increased for all of these commonly reported GERD symptoms when on treatment, compared to baseline, which provides some additional descriptive data in favor of treatment providing symptom control.

Rescue Medication Use:
During the baseline period (days -8 to -2), the mean number of days without rescue medication use was 4.8/7 (69%), and was similar to a mean of 70% during the 4 week treatment period. Rescue medications included study provided antacids (magnesium or aluminum hydroxide), and patients were instructed that they could be used as needed per product labelling. Although the mean use was similar between the baseline and treatment periods, the use of medication and reports of symptoms did vary with time. This reviewer performed her own exploratory analysis to evaluate when rescue medication was used in relation to heartburn symptoms throughout the study duration. The figure below illustrates a trend toward increasing frequency of patient reports of heartburn, as well as rescue medication use during the screening period (when all patients were off acid suppressing therapy). Then, during the open label treatment (starting on Day 1), it is notable that reports of heartburn trended downward, as did use of rescue medications.

Figure 3: Rescue medication and Heartburn reported, vs time



(source: reviewer's analysis, created from data provided in sNDA22287 application, received 9/30/15, using ADEFF dataset, study 206).

Overall, this exploratory analysis demonstrates that while the mean percent of days where rescue medication was used was low overall, the reports of heartburn and rescue medication use decreased steadily as the treatment period progressed, supporting the effectiveness of dexlansoprazole for the control of sGERD symptoms.

6.1.7 Subpopulations

Subgroup analyses by age and race were not performed, as the patient population was limited to patients 12 to 17 years of age based on the requirements of the PMR, and the population was 91% Caucasian. Therefore, a subgroup analysis based on age or race

would not be meaningful due to the already limited age group and homogeneous Caucasian population. However, a subgroup analysis based on sex was performed.

For the primary efficacy endpoint, percentage of days with neither daytime or nighttime heartburn during treatment, there was no meaningful difference between males and females. Females reported a median 44% days without daytime or nighttime heartburn, and males reported 57% days without daytime or nighttime heartburn. The lack of difference in efficacy based on gender is consistent with what is known for this drug class.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study 206 evaluated a single dose, 30 mg daily, which is the approved dose for the treatment of sGERD in adult patients. The PK profile for this formulation was previously evaluated in this patient population (12 to 17 years of age) in study T-P107-163, and the PK findings in pediatric patients were similar to those in adults. Given these similarities, the applicant chose the dose that is approved for this indication in adults, to be administered to this adolescent study population. Of note, two doses (i.e., 30 mg and 60 mg) were evaluated against placebo in the adult trials that supported approval and product labeling and the 60 mg daily dose did not offer additional clinical benefit over the 30 mg once daily dose. For this reason, this reviewer concludes that the choice of a single 30mg dose was appropriate for this pediatric study. Refer to clinical pharmacology review, by Dr. Shen Li, for further details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No data were collected regarding the persistence of treatment effect after the treatment period. No data were provided regarding the need to resume medical therapy after conclusion of the study. In Figure 3 above, when observing the number of reports of heartburn over time, this reviewer notes that reports of heartburn appear to decrease as the treatment period progressed, suggesting that overall patients were improving as treatment continued. However, the trial was not designed to quantify this effect, so limited conclusions can be drawn from this illustration.

6.2 Indications 2 and 3 – Healing of all grades of Erosive Esophagitis (EE), Maintaining Healing of EE, and Control of Heartburn

Results of study 207 were submitted to support the claim that Dexilant 60mg once daily promotes healing of erosive esophagitis in pediatric patients 12 to 17 years of age, and Dexilant 30 mg daily vs placebo for an additional 4 months promotes maintenance of healed EE and relief of heartburn.

The primary endpoint was safety, and the secondary aim was to assess efficacy, based on the crude rate of healing of EE at week 8, the crude rate of maintained healing at

week 24, and the percentage of 24 hour heartburn free periods over the course of treatment. The efficacy data is discussed below, with a detailed safety analysis in section 7.

6.2.1 Methods

Extrapolation of Efficacy:
The use of Dexilant in this age group for the treatment of erosive esophagitis is supported by evidence from adequate and well-controlled studies of Dexilant capsules in adults, and by safety and pharmacokinetic studies performed in pediatric patients. Efficacy will be partially extrapolated from adequate and well-controlled trials conducted in adults to support the pediatric indications of healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and control of heartburn symptoms. The pathophysiology of erosive esophagitis and response to therapy is sufficiently similar between adults and patients 12 to 17 years of age to support partial extrapolation of efficacy for these indications. Based on the results of PK studies, the exposure-response is expected to be similar between pediatric patients and adults. Therefore, efficacy can be extrapolated from adult trials. Partial extrapolation requires the comparison of a pharmacodynamic (PD) measure that can be used to determine efficacy. Though intragastric pH was not measured directly in this study, efficacy was assessed using an objective measure (endoscopic healing) to document clinical effect. Endoscopic assessment of the esophageal mucosa to determine whether the erosions had healed was the same measure utilized in the adult trials. For symptom control, the Division previously determined that patient reported heartburn, collected via age-appropriate questionnaires (e.g., as recorded in the electronic daily diary) and used to calculate the measure of 24 hour heartburn free periods, was acceptable to assess the control of heartburn symptoms.

Study 207 was designed in a similar fashion to the adult trials for these indications, to facilitate partial extrapolation of efficacy. Refer to section 5.3.2 above for detailed discussion of study procedures. The relevant efficacy data are summarized in this section, with a detailed safety analysis in section 7.

6.2.2. Demographics

Sixty-three patients were initially enrolled from 18 sites worldwide, but one patient never started treatment; therefore, 62 patients were treated during this trial. Patients were recruited from study sites in the United States (8), Poland (6), Portugal (3), and Mexico (1). The mean age was 14.8 years (range 12-17 years), and slightly more males (61.3%) were enrolled compared to females (38.7%). The population was primarily Caucasian (98.4%) and consisted mostly of patients with grades A and B esophagitis (97%), as measured by the Los Angeles Classification. Refer to Table 28 for details of LA grading scale. Demographic data are summarized in Table 8 below.

Table 8: Demographics from Study 207

	Initial Treatment Phase (Open Label)	Second Phase (Double Blind, placebo controlled)	
	Dexlansporazole 60mg QD N=62	**Placebo N=26**	**Dexlansoprazole 30mg QD N=25**
Age (years)			
Mean ± SD	15 ± 2	5 ± 2	15 ± 1
Median (range)	15 (12, 17)	15 (12, 17)	15 (12, 17)
12-14 (n, %)	24 (39)	11 (42)	10 (40)
15-17 (n, %)	38 (61)	15 (58)	15 (60)
Gender (n, %)			
Female	24 (39)	10 (39)	11 (44)
Race			
Black/African American	1 (2)	1 (4)	0
White	61 (98)	25 (96)	25 (100)
Weight (kg)			
Mean (SD)	62 (17)	61 (16)	165 (7)
Median (Min, Max)	60 (26, 113)	59 (34, 96)	59 (36, 103)
Baseline EE grade[1]			
A	34 (55)	16 (62)	14 (56)
B	26 (42)	9 (35)	11 (44)
C	1 (2)	1 (4)	0
D	1 (2)	0	0

[1] *See Appendix, Table 28 for details of grading scale, based on LA classification*
(source: reviewer's table, adapted from applicant's provided Table 11.b, clinical study report for study 207, (page 76)) .

The patient population in this study was well distributed across the age ranges of interest which allows for generalization of the trial results to the larger patient population with EE who are between 12 and 17 years of age. The population was predominantly white/Caucasian, with only one non-white patient enrolled. Ethnicity data (Hispanic or Latino, vs non-Hispanic/Latino) were collected only for patients at US sites. Six of 62 (9.7%) enrolled patients were Hispanic. This may limit the applicability of this data to other races; however differences in baseline acid suppression and response to therapy based on ethnicity are not well characterized. Of note, in the subgroup analysis conducted for the adult trials that supported approval, race or ethnicity did not have a significant impact on safety or efficacy. However, literature suggests that there may be differences in response in Japanese patients compared with other populations, which

may be based on CYP2C19 metabolizer status.[9] Of note, efficacy was not evaluated by metabolizer status but only 2 pediatric patients were found to be "poor metabolizers" and there was no difference in safety based on metabolizer status. Overall it is the opinion of this reviewer that the study demographics are sufficiently representative of the population that will use the drug in the United States.

The majority of patients in the study had mild to moderate (Grade A-B) EE, with only two patients having more severe disease. This is reflective of the pediatric population with EE where grade C-D erosive esophagitis is uncommonly diagnosed in pediatric patients.[10, 11, 12]

6.2.3. Patient Disposition

Sixty-three patients were enrolled but one patient was non-compliant with taking the study drug; therefore, this patient was discontinued from the study due to non-compliance, and was not included in analysis, since no study drug was ever administered. Therefore, 62 patients were included in the efficacy analyses.

Of the 62 patients who received dexlansoprazole 60mg daily, 58 patients completed the 8-week open label treatment phase. Four patients discontinued early (summarized in Table 9 below). At the conclusion of the open-label portion of the study 7/58 (12%) patients did not have documentation of healing of EE, and were ineligible to continue to the blinded maintenance phase of the study.

Of the 51 patients who were randomized into the double- blinded maintenance phase, 26 were randomized to placebo and 25 to treatment with dexlansoprazole 30mg daily. Thirty-eight of 51 (75%) patients completed the maintenance phase of the study.

The reasons for early discontinuation are summarized in Table 9 below.

9 Saitoh T, Otsuka H, Kawasaki T, et al. Influences of CYP2C19 polymorphism on recurrence of reflux esophagitis during proton pump inhibitor maintenance therapy. Hepatogastroenterology. 2009.
10 Yamamoto E, Brito HS, Ogata SK, et al. High rate of clinical and endoscopic relapse after healing of erosive peptic esophagitis in children and adolescents. J Pediatr Gastroenterol Nutr. 2014 Nov; 59(5): 595-9.
11 Boccia G, Manguso F, Miele E, et al. Maintenance therapy for erosive esophagitis in children after healing by omeprazole: is it advisable? Am J Gastroenterol 2007; 102:1291-97
12 Tolia V, Youssef N, Gilger M, et al. Esomeprazole for the treatment of erosive esophagitis in children: an international, multicenter, randomized parallel-group, double blind (for dose) study. BMC Pediatrics. 2010;10:41.

Table 9: Reasons for Early Discontinuation, Study 207

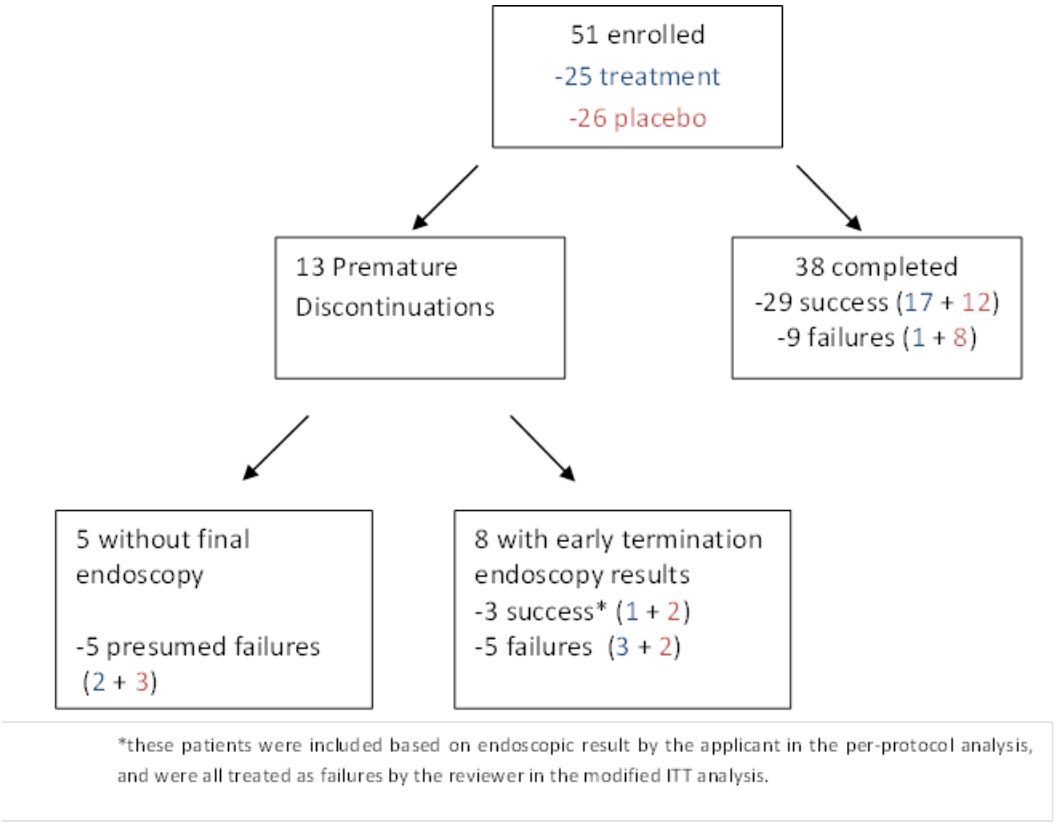
	Open Label Phase	Double Blind Phase	
	60 mg dex N=62 n (%)	Placebo N=26 n (%)	30mg dex N=25 n (%)
Pretreatment event / or AE	1 (2%)	0	1 (4%)
Major protocol Deviation	1 (2%)	0	0
Lost to Follow-up	1 (2%)	0	0
Lack of Efficacy[1]	1	5 (19%)	2 (8%)
Voluntary Withdrawal, not specified as related to efficacy	0	1	4

[1] *Lack of efficacy includes patients reported as voluntary withdrawal due to "no improvement or return of symptoms," and the AE of "EE".*
(source: reviewer's analysis, adapted from Table 10.a "Reasons for Premature Discontinuation from Study Drug), and incorporating additional details as provided in footnote 1, applicant provided clinical study report for study 207, page 69/107)

A greater number of patients withdrew for reasons related to lack of efficacy (5/26, 19%) in the placebo arm, than in the treatment arm (2/25, 8%), which is consistent with benefit derived from the drug. One patient was discontinued due to major protocol deviation (a diagnosis of eosinophilic esophagitis discovered after enrollment). This patient discontinued participation at day 20 of treatment, and did not have endoscopic results that were included in the efficacy data calculations for healing.

Figure 4 below highlights the disposition of patients throughout the double-blind, maintenance phase of study 207.

Figure 4: Patient Disposition in Study 207, Double Blind Maintenance



(source: reviewer's analysis, based on applicant's data from ADFA dataset, and Appendix D from applicant's response to information request, received 3/10/2106.)

Handling of early terminations as it pertains to calculation of the efficacy endpoint is discussed in section 6.2.5 below.

6.2.4 Analysis of Primary Endpoint(s)

The primary endpoint of the study was a safety endpoint, treatment emergent adverse events (TEAEs) experienced by ≥5% of patients. As this is a safety endpoint, it will be discussed in depth in section 7.

6.2.5 Analysis of Secondary Endpoint(s)

The main efficacy endpoints for the study included 1) percentage of patients with EE who healed at 8 weeks, 2) percentage of patients healed at 8 weeks who remained healed at the conclusion of the double blind maintenance phase and 3) percentage of days with no daytime or nighttime symptoms reported, for each phase of the study.

Percentage of patients with Healed EE after 8 weeks treatment:

Sixty-two patients with endoscopically confirmed EE were enrolled and treated with dexlansoprazole 60mg daily. Fifty-eight of the 62 (94%) patients completed the 8 week treatment phase. After 8 weeks treatment, 51/58 (88%) patients were healed. This rate of healing is comparable to the rate of healing documented in the trials conducted to support product labeling in adults with this same dose (85-87% in adults).[13] The adult patients also had a preponderance of Grade A-B esophagitis (71%) compared with Grades C-D (29%), though this difference was more pronounced in the adolescents, (97% with Grade A-B) as discussed above. Given that pediatric patients generally have more mild disease compared to adult patients with EE, this reviewer concludes that the difference in severity of disease, based on LA grade, between populations does not impact the ability to determine the efficacy of dexlansoprazole for the healing of EE at week 8.

There were an insufficient number of patients with Grades C-D to determine if there are differences in healing based on initial LA grade. The one patient with grade C did heal at week 8, and was later randomized to placebo, however, did not maintain healing to week 24. The one patient with Grade D at baseline did not heal at 8 weeks, but showed improvement to Grade B after 8 weeks of therapy.

This reviewer notes that 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. The reasons for early discontinuation above were not all well-defined, and some of those patients may have discontinued due to treatment failure. A more conservative analysis based on intention to treat principles would calculate the rate of healing as 51 patients who were healed, out of the 62 patients who started treatment. This type of analysis would provide a rate of healing of 82%. However, this number is generally similar to the rate of healing as calculated based on the pre-specified statistical plan (88%). Therefore, this reviewer concludes that this difference does not change the overall conclusions drawn from the data. Refer to statistical review by Dr. Andrejus Parfionovas (primary reviewer) and Dr. Yeh-Fong Chen (secondary reviewer) for further detail.

Maintenance of Healing of EE (week 8 through week 24):

As described above, 51/58 (88%) patients achieved healing of EE at week 8, documented by endoscopy and evaluated on the LA scale. Healed patients were then randomized to receive either dexlansoprazole 30 mg daily or placebo for 16 additional

13 Approved product labelling for Dexilant, updated 2/2/2016, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022287s020lbl.pdf

weeks. Patients were reassessed by endoscopy at study week 24, to determine the percentage who remained healed. The following table summarizes the endoscopy results at week 24.

Table 10: Week 24 results for Maintenance of Healing

	Placebo (N=24)	**Dexlansoprazole 30mg (N=22)**
Maintained Healing n, (%)[1] (95% CI)	14 (58) (37-78)	18 (82) (60 – 95)

[1] *% patients who maintained healing was based on those who had week 24 / early termination visit scope data available.*
(source: reviewer's table, based on data from applicant's 15.2.1.2, page 180 of clinical study report for study 207)

The crude rate of healing calculated by the applicant, as described in the pre-specified statistical analysis plan, was derived from data of "evaluable patients", rather than a strict intention to treat (ITT) analysis. The percentage of patients who maintained healing as described above is based on the total number of patients who had evaluable results at week 24. Evaluable patients included those who received at least one dose of study drug, and had a post-baseline endoscopy. Eight of the 13 patients who discontinued study drug prematurely did have a final endoscopy at the time of early termination. See Figure 4 above. Those endoscopies were done within reasonable proximity to the end of the treatment window (between day 120 and 168) and so the applicant included that data when calculating week 24 results. From a clinical perspective, this reviewer considers this to be reasonable handling of the early termination data. Patients who did not consent to a final endoscopy were not included in this analysis. This calculation is similar to the method used to analyze the data in the adult trials which supported the initial approval and product labelling for the adult indications.

The data demonstrate a higher rate of maintenance of healing in those who received maintenance treatment for 4 months (82%), compared with placebo (58%). This small trial was not powered to detect a statistically significant difference between treatment groups. However, the proportion of patients who maintained healing on treatment was numerically greater as compared with placebo. In the adult trials that supported approval, adults were treated for 6 months for maintenance of healing, and 66% of patients maintained healing in the treatment group, vs only 14% in the placebo group ($p<0.00001$).[14] The high rate of maintenance of healing in the placebo group in this pediatric study may be in part due to the shorter duration of follow-up. In the adult trial, the placebo rate of maintenance of healing declined steadily over time (43% at 1 mo,

14 Approved product labelling for Dexilant, updated 2/2/2016, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022287s020lbl.pdf

23% at 3 months, and 14% by 6mo).[15] The adult trials were adequately powered. While the placebo rate observed in the pediatric trial is greater than the placebo rate reported from the adults trials, the pediatric patients had milder disease overall and the primary efficacy endpoint assessment (endoscopy) was conducted at an earlier time point (4 months in the pediatric trial vs 6 months in the adults trials). These factors likely contributed to the higher placebo rate in the pediatric patients.

This reviewer notes that in study 207, more than half the patients who received placebo maintained healing of their EE. Further analysis of the data, provided by the applicant in a response to information request, demonstrated that patients with more severe disease (LA grade B, C or D, when compared with grade A) were more likely to experience recurrence of EE. Though the rates of maintaining healing were similar regardless of treatment for those patients with grade A disease (81% maintained healing at week 24 on treatment, 87% on placebo), the difference was more pronounced in patients with grade B disease at enrollment (81% for those on treatment, compared with 13% for those on placebo). This difference supports the conclusion that maintenance therapy is indicated to maintain healed EE, and suggests that maintenance therapy is most important in patients with more severe initial disease. This reviewer concludes that maintenance therapy is of benefit for these pediatric patients.

This reviewer notes that the applicant's calculation of the crude rate of maintained healing was done using last observation carried forward (LOCF) treatment of missing week 24 endoscopy data, and was not strictly an intention to treat (ITT) analysis. This reviewer conducted an additional modified ITT analysis, utilizing all available clinical data. Accepting that the LOCF treatment was reasonable for the 8 patients who discontinued early, as most occurred close to 24 weeks, (early termination endoscopies were performed between study day 120 – 168), and applying ITT principles, with the assumption that patients without an early termination endoscopy were treatment failures, this reviewer calculates the rate of maintained healing as 14/26 (54%) in placebo, and 18/25 (72%) in the treatment arm.

This reviewer then conducted an additional sensitivity analysis to assess the effect of the LOCF assumption. In this analysis, the reviewer explores the possibility that recurrence of EE could occur late in the maintenance period. For example, if a patient discontinued the study at week 18, and ET endoscopy demonstrated maintenance of healing at that time, it is possible that recurrence may have occurred, had the patient been followed through to week 24. For the early terminations with endoscopy data, 2 patients demonstrated maintained healing at early termination (ET) endoscopy in the placebo group (done at day 149 and day 161). In the dexlansoprazole group, 1 patient maintained healing at ET endoscopy (done at day 149).[16] If these patients are

15 Clinical review for Dexilant, NDA 22287, by Dr. Keith Amand, dated 8/29/2008
16 Timing of post-baseline endoscopy that was treated as the week 24 evaluation were derived by the reviewer from applicant's provided ADFA dataset for study 207.

conservatively counted as failures in the ITT analysis, then the percentage of patients who maintained healing is 12/26 (46%) in the placebo group, and 17/25 (68%) in the treatment group.

In conclusion, the ITT analysis demonstrates a smaller difference between placebo and treatment groups, and a lower rate of maintained healing, compared with the pre-specified crude healing rates. Even utilizing the most conservative estimate of maintaining healing in the pediatric patients (68%), the results are still similar to those seen in the adult trials (66%). Though the rate of maintained healing in the placebo group was somewhat high, the fact that more patients in the dexlansoprazole group maintained healing, compared with placebo, provides some additional confidence that treatment provides benefit in this age group. Acknowledging that efficacy is being partially extrapolated from adult data, and the limitations of a small, non-powered trial, as previously discussed, this reviewer finds that the data support approval of the indication of maintaining healing of EE in pediatric patients 12 to 17 years of age.

Supportive efficacy measures during the 12 week post-treatment follow-up period are discussed below in section 6.2.5.

% of Days with Neither Daytime nor Nighttime Heartburn Reported

The current indication for the maintenance of healing of EE in adults includes control of heartburn for patients receiving maintenance therapy for EE. In the pediatric trial, reported heartburn was collected directly from patients and recorded in daily electronic diary (eDiary) entries (see Appendix, Figure 8 for eDiary questions). Refer to section 5 above for additional details. Control of heartburn symptoms was assessed throughout the trial by the median percentage of heartburn free 24hr periods. This measure is analogous to that used in the adult trials to support approval.

All patients were symptomatic during the 7 day screening period, reporting the number of heartburn free 24 hour periods ranging from 0 to 6, with a median of 1/6 heartburn-free 24 hour periods. In the initial treatment phase, patients demonstrated a meaningful improvement in the median percentage of heartburn free 24 hour periods. At baseline, the percentage of heartburn free 24 hour periods was 14% (calculated based on 7 day screening period eDiary data) and increased to 66% over the 8-week open label treatment for healing of EE.

During the 16-week maintenance phase, patients who received dexlansoprazole 30 mg showed continued improvement in the median percentage of 24 hour heartburn free periods during maintenance (week 8-24) to 87% compared with 68% in the placebo group. There was minimal additional improvement in heartburn free periods in the placebo group, but the dexlansoprazole-treated group appeared to gain further benefit from continued treatment after the initial healing of EE. This reviewer notes several key differences when comparing control of heartburn during the maintenance phase of the

adult trials vs the maintenance phase of the pediatric trial. The median percentage of heartburn free 24 hour periods was 96% based on adults patients who received the 30mg daily dose for maintenance of healing of EE, compared with 29% of patients receiving placebo. Though the pediatric data are less compelling since the difference between the dexlansoprazole group and placebo group is smaller, it is notable that in the adult trial, the majority of patients in the placebo arm dropped out prior to the conclusion of the maintenance phase (full data available for only 23/141 patients). The fact that the adult population had more severe disease at baseline may have affected adult patients' ability to tolerate the placebo arm of the trial. In contrast, in this pediatric trial, patients generally did well even in the placebo arm. This may be a result of differences in underlying disease severity, rates of recurrence off treatment, or duration of disease, rather than effectiveness of Dexilant in control of heartburn symptoms. Furthermore, while the placebo group reported a high rate of heartburn-free days in the pediatric trial, 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 supports that symptoms remained well-controlled during the maintenance phase.

The additional exploratory data assessing control of heartburn symptoms in EE is discussed below in section 6.2.6.

6.2.6 Analysis of Additional Exploratory Endpoint(s)

Electronic Diary Entries throughout Study 207:

Electronic diary entries were collected throughout the duration of the trial, from baseline through the end of follow-up or final study visit. Measures assessed during each phase of the study include the percentage of 24 hour periods without daytime or nighttime heartburn, but also daytime control of heartburn, and nighttime control of heartburn independently. As the proposed indication for control of heartburn applies only to the maintenance period, the following discussion focuses on those data. Table 11 below summarizes the exploratory eDiary data on symptom control.

Table 11: Summary of Patient Reported Data from eDiaries

	Baseline[1] (screening period (day -8 to -2) % Days without symptom	60mg dexlansporazole (open label phase, week 1-8) N=62	30mg dexlansoprazole (during maintenance phase, week 8-24)	Placebo (during maintenance phase, week 8-24)
% Days without daytime heartburn				
Mean ±SD	32 ± 29	66 ± 28	80 ± 28	74 ± 24
Median	29	74	90	83
Range	(0,100)	0,100	0,100	12,100
% Days without nighttime heartburn				
Mean ±SD	49 ± 34	76 ± 26	84 ± 28	85 ± 17
Median	43	85	96	90
Range	(0,100)	0,100	0,100	42,100

(source: reviewer's analysis, data provided in aplicant's response to information request received 6/10/2016, and summary results from clinical study report for study 207, tables 11k (pg 84) and 11i (pg85).)

The eDiary data were collected to demonstrate the ability of dexlansoprazole to control heartburn symptoms in patients with EE. The applicant divided the data to look at daytime and nighttime symptom control separately. For each measure, symptom control improved markedly from baseline in the first 8 weeks. In the subsequent maintenance phase, there was minimal difference in symptom control during the maintenance period between patients receiving treatment vs placebo. This reviewer notes overall that that control of symptoms is markedly better over weeks 8 - 24 as compared with baseline reported frequency of symptoms, and slightly improved over the symptoms reported over the first 8 weeks. This may suggest that majority of the improvement in heartburn symptom control is attributed to healing of the underlying EE. Once healed, the data for the 24 hour heartburn free periods supports some measure of added benefit from treatment, as discussed above, though the additional benefit may be small. In the opinion of this reviewer, breaking the data down into daytime only symptoms or nighttime only symptoms does not provide additional supportive evidence of efficacy in the control of heartburn symptoms. Given the mechanism of action of dexlansoprazole (irreversible inhibition of gastric parietal cell acid secretion) the overall acid control should be fairly stable over a 24 hour period. For this reason, this reviewer gives greater weight to the 24 hour heartburn free period measure in the analysis of benefit.

Heartburn Severity based on eDiary entry:

The mean severity of pain from heartburn was also assessed in the daily eDiary entries. Pain severity was recorded on a scale of 0 to 3 where 0=no pain, 1=did not hurt very

much, 2=hurt some, and 3=hurt a lot. The numeric score was averaged over the treatment period. The reported baseline (day -8 to -2) mean degree of heartburn pain for daytime/nighttime combined was 1.03 (rage 0.1 – 3). During the open label treatment phase (through week 8), the mean value was 0.5 (range 0-3). By the maintenance phase (week 8 -24), the value was 0.4 (range (0-1) for the placebo group, and 0.3 (range 0-2)) for the treatment arm. Similar to the measure of heartburn free days, these data suggest that improvement occurred mostly between baseline and establishing healing of EE. The differences reported in pain by the maintenance phase were minimal between placebo and treatment arm. The reason for that may be that most of the patients were well healed by this point, and symptoms are associated with active erosions.

Pediatric Gastroesophageal Symptom Questionnaire (Adolescent, Short Form):

The PGSQ-A questionnaire is a 35- item instrument developed to assess GERD related symptoms and the impact of symptoms on adolescents' quality of life. The tool used in this study was a shortened, 11 item version, which used questions that focused on the frequency of GERD symptoms and their related impact (Refer to Appendix, Figure 7, for the content of the PGSQ-A-SF). Patients completed this survey at each scheduled clinic visit. Each item is scored on a scale of 1 to 5. Lower scores indicate symptoms present on fewer days, and/or less impact of symptoms on quality of life. The tool assesses symptoms over a 7 day recall period, and results are provided as an average score for "symptoms" and "impact of symptoms." The following table summarizes results from the PGSQ-A-SF.

Table 12: Summary of Mean PGSQ-A-SF scores before and during treatment

	Screening Mean (SD)	**Open Label Healing (week 8) 60mg Dex Mean (SD)**	**Maintenance (week 24) 30mg Dex Mean (SD)**	**Maintenance (week 24) Placebo Mean (SD)**
Mean PGSQ-A-SF symptom subscale score	2.2 (0.69)	1.6 (0.55)	1.4 (0.37)	1.4 (0.4)
Mean PGSQ-A-SF Impact subscale score	2.4 (0.9)	1.7 (0.91)	1.5 (0.76)	1.5 (0.86)

(source: reviewer's analysis, from applicant provided tables 11.c (page 77 in clinical study report, study 207), and Tables 15.2.3.1.2, and 15.2.3.1.3 (pg 203/204, clinical study report, study 207))

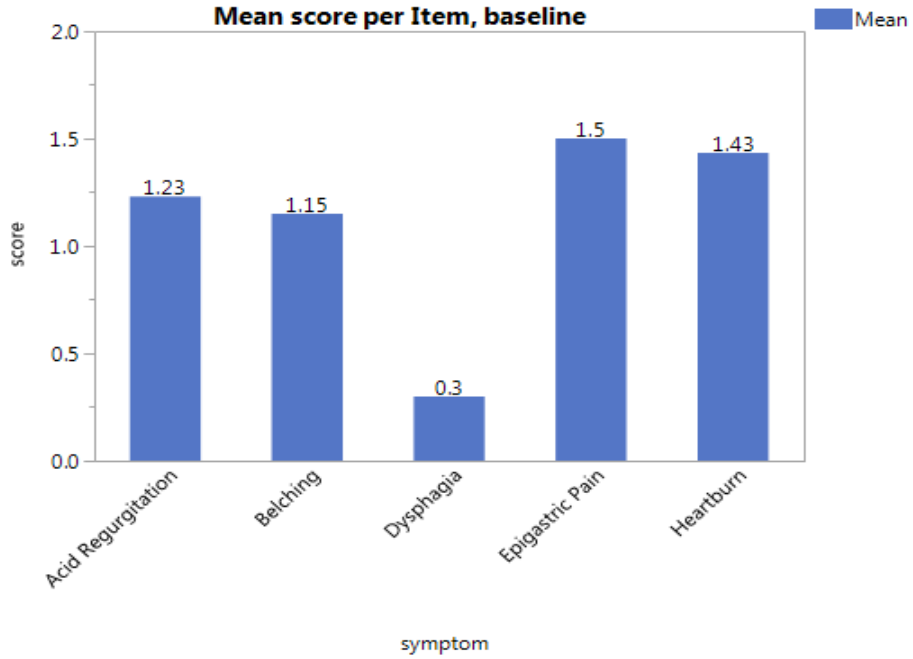
Overall, there was a noted decrease in scores from the screening period to week 8 (mean decrease was 0.6 for symptom, and 0.7 for impact). The lower scores did persist into the maintenance phase, even in those patients who received placebo, again supporting that the improvement is likely mostly related to healing of the initial EE. These findings are considered exploratory, as this tool is not qualified for the purposes of supporting labeling claims.

Investigator Assessment of GERD Symptom Severity:

An investigator assessment of GERD symptom severity was recorded at each scheduled visit. The definitions used to standardize this assessment are summarized in the Appendix, in Table 27.

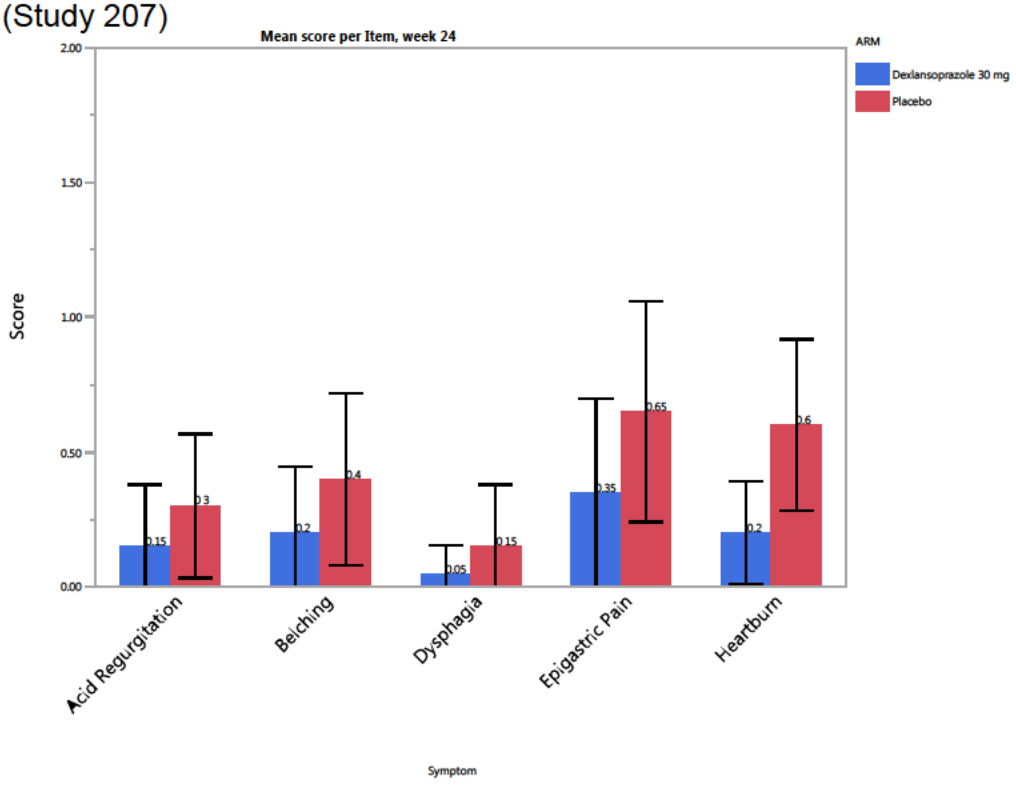
The severity was coded as 0=none, 1=mild, 2=moderate, 3=severe, 4= very severe. The severity of all the symptoms did improve somewhat from baseline. The following graphs demonstrate the mean scores for each symptom, at baseline, and at week 24 (by treatment arm). Overall there was a decrease in symptom severity from baseline. However, by week 24, the difference in symptom severity between treatment groups was minimal.

Figure 5: Mean Severity Scores for Investigator GERD Assessment (Study 207)



(source: reviewer's analysis, demonstrating mean severity scores at baseline for each item in investigator assessment of GERD, derived from data provided in applicant's sNDA22287 submission, dated 9/30/15, ADGERD dataset, study 207).

Figure 6: Mean Severity Scores for Investigator GERD Assessment, by Treatment Arm (Study 207)



Each error bar is constructed using a 95% confidence interval of the mean.
(source: reviewer's analysis, demonstrating mean severity scores for each component at week 24, by treatment arm, derived from data provided in applicant's sNDA22287 submission, dated 9/30/15, ADGERD dataset, study 207).

While the data support that there was overall improvement in symptom control by treating EE, these instruments do not support a claim for continued benefit of maintenance therapy after healing, on control of heartburn symptoms. Additionally this measure is of limited utility, as it has not been qualified for the purposes of supporting a labeling claim, and it introduces additional bias as this is an investigator reported measure. The assessment of symptom severity by an observer is less reliable and more subjective than similar information collected from direct report from the patient.

In the opinion of this reviewer, the data obtained directly from patients from the eDiary recorded symptoms provides more reliable data to support the efficacy of dexlansoprazole to control heartburn symptoms in patients with EE.

6.2.7 Subpopulations

Given that the population was already a narrow age range (pediatric patients 12-17 years of age), and nearly all patients were Caucasian, there were no analyses performed based on age or race. Efficacy was assessed for difference by sex. No differences in efficacy based on sex are evident based on the available data, though the small numbers limit the utility of these comparisons. For healing of EE at week 8, healing was documented in 96% [95% CI (77, 100)] of females, and 83% [95% CI (67, 94)] of males. At week 24, females on treatment maintained healing 78% of the time, compared with 85% of males on treatment. Placebo rates of maintaining healing were also high (70% for females on placebo, vs 50% for males). See statistical review by Dr. Andrejus Parfionovas (primary reviewer) / Dr. Yeh-Fong Chen (secondary reviewer), for further discussion.

In addition, analysis of efficacy based on EE grade was completed, demonstrating greater clinical benefit from maintenance therapy in patients with higher grade EE (grade B) when compared with grade A. Refer to section 6.2.5 for further discussion.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study 207 evaluated one dose for each indication, 60 mg daily for healing of EE and 30 mg daily vs placebo for maintenance of healing and control of heartburn. The selected doses are the same doses approved for adults for each indication. Refer to section 6.1.8 and clinical pharmacology review by Dr. Shen Li for further discussion.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of Efficacy after Healing Treatment:
Fifty one patients were randomized to the maintenance phase at week 8. Of those patients, 6 patients were early withdrawals from the placebo group, and 7 patients from treatment group. Refer to section 6.2.3 for further discussion. Lack of efficacy/need for alternate therapy was the reason for study withdrawal for 4 patients in placebo as compared to only 1 in the treatment group. While the overall numbers are small, this may suggest that there are patients who benefit from maintenance therapy as there were a larger number of patients in the placebo group who dropped out due to lack of efficacy.

Follow-up off treatment (week 24-36)
At the conclusion of the maintenance treatment period (week 24), patients who maintained healing were followed, off treatment, for an additional 12 weeks, or until symptoms returned which required treatment (endoscopy or re-initiation of acid suppression therapy). Follow-up was conducted by monthly clinic visit at weeks 28, 32, and 36. In addition, patients continued to complete daily eDiary recording of symptoms.

Investigator's assessment of GERD and patient response to PGSQ-A-SF were completed at week 28, 32, and 36 visits.

Thirty two patients maintained healing at the conclusion of the maintenance period and 27 patients (16 treated with Dexilant and 11 placebo) continued into the 12 week follow-up period. During the follow up period only 1/27 (4%) patient had reoccurrence of GERD symptoms and required treatment with PPI (omeprazole). This patient had received treatment with 30 mg dexlansoprazole during the double blind maintenance phase.

The percentage of 24 hour heartburn free periods remained high (84% for those previously on placebo, 86% for those previously on dexlansoprazole), suggesting that patients did not have recurrence of heartburn symptoms once healing was achieved. Furthermore, once therapy was discontinued in patients who maintained healing, there was a low rate of recurrence of symptoms. The median severity scores from the eDiaries for heartburn pain for all periods during follow-up remained low at ≤0.2. The percentage of days without rescue medication use remained high during the follow-up period (96% in those previously on placebo, 94% for those previously on treatment), suggesting that most patients continued to have well-controlled symptoms. The totality of these measures suggest that for patients who maintained healing of EE, there was a continued benefit of symptom control after treatment was discontinued.

7 Review of Safety

Safety Summary:

Overall, the safety profile of dexlansoprazole in pediatric patients 12 to 17 years of age was demonstrated to be similar to the safety profile that has been demonstrated in adult patients in large clinical trials. There were no new safety signals identified in the trials submitted in this efficacy supplement.

Two pediatric clinical trials were included in this efficacy supplement, which contained safety data. Study 206 enrolled a total of 104 patients in the safety population, and Study 207 enrolled 62 patients in the safety population. Enrolled patients in these trials were aged 12 – 17 years inclusive. Safety data from these two trials was evaluated separately, as the two trials enrolled different patient populations, used different dosing regimens, and differing durations of treatment. A combined analysis was also performed to assess the overall most common adverse events seen across dosing regimens.

There were no deaths in either study. There were no serious adverse events (SAE) in study 206. In study 207, 4/62 (7%) patients experienced a SAE (2 in the treatment group and 2 in the placebo group). No unique SAE was reported in more than one

patient. These SAEs included erosive esophagitis and seizure like episodes in the treatment group (both occurring during the double blind phase at the lower dose) and influenza infection and intentional ingestion 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 relatively common in both trials, but 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 ≥5% of patients were abdominal pain, diarrhea, and headache. In study 207, TEAEs occurred with greater frequency, though it is important to note the patient numbers were small. In the open label phase (Dexilant 60 mg), 38/62 (61%) patients experienced at least one TEAE. The most commonly reported TEAEs seen in ≥5% of patients were headache, oropharyngeal pain, nasopharyngitis, abdominal pain, diarrhea, pharyngitis, and respiratory tract infection. In the double blind phase (Dexilant 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 ≥5% of patients and greater than placebo were headache, pharyngitis, sinusitis, insomnia, respiratory tract infection, and bronchitis. In the combined analysis, the most common TEAEs, seen in ≥5% patients overall were headache, abdominal pain, diarrhea, nasopharyngitis, and oropharyngeal pain.

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

In summary, dexlansoprazole was well tolerated at both 30 mg and 60 mg daily doses in pediatric patients 12 to 17 years of age enrolled in the two trial populations. There were no unexpected safety signals identified in this population, and use of dexlansoprazole for symptomatic GERD and erosive esophagitis and control of heartburn symptoms in adolescents has a favorable risk-benefit profile.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Results of studies 206 and 207 were submitted to evaluate the safety of dexlansoprazole in adolescent patients. Refer to section 5 for detailed description of study design and safety assessments conducted. This section will focus on the safety review.

7.1.2 Categorization of Adverse Events

The primary safety outcome evaluated in both studies was the presence of treatment-emergent adverse events (TEAEs) experienced by ≥5% of subjects while receiving

dexlansoprazole. Additional safety parameters assessed included basic laboratory parameters, vital signs, and physical examination findings.

A treatment emergent adverse event (TEAE) was defined as an adverse event (AE) that started or worsened after the first dose of medication, and occurred no more than 30 days after the last dose was ingested. MedDRA version 17.0 terms were utilized, and AEs were categorized by system/organ class, high level term, and preferred term.

This clinical reviewer compared verbatim terms with the applicant's coded/preferred term to ensure consistency in coding and revised as needed. Overall, this clinical reviewer's analysis was similar to the applicant's analysis, but the following adjustments were made by the clinical reviewer prior to re-analysis of the safety data:

Study 206: Abdominal discomfort (1), abdominal pain upper (4), and abdominal pain lower (1) are grouped together with "abdominal pain." Additionally oral herpes (2) is combined with "herpes simplex."

Study 207: In the open label phase, upper respiratory tract infection (2) is combined with "respiratory tract infection," and abdominal pain upper (1) is combined with "abdominal pain." In the double blind phase, abdominal pain upper (3) was combined with "abdominal pain" and upper respiratory tract infection (1) is combined with "respiratory tract infection."

AE reports were solicited by investigators at each study visit. The patient was asked a neutral question, such as "How have you been feeling since your last visit" and given the opportunity to report any symptoms. Subjects also may have reported AEs at other times during the study. All AEs reported were documented in the eCRF, regardless of determination of causality.

Criteria for serious AEs were clearly defined prior to the start of the study, and any serious AE (SAE) was required to be reported to Takeda within 24hr. There were no SAEs in study 206. Those occurring in study 207 are discussed in section 7.3.2.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Cross-study comparisons are of limited value for these indications, as the dosing, duration, and underlying disease differed between the two trials; therefore, this reviewer evaluated safety data from studies 206 and 207 separately. Adverse events are summarized both by individual study and as pooled data due to low total number of subjects.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The doses and duration of treatment evaluated in both study 206 and study 207 are adequate to evaluate the safety of the intended use of this product.

For study 206, mean exposure was 30 days (±4 days). Most patients were highly compliant with 57/104 (55%) taking the specified dose for at least 29 days and 45/104 (43%) patients taking the dose for between 22-28 days out of the four week treatment period. Given that the intended treatment course is one month, and patients do forget doses intermittently, these data reasonably approximate exposure that would be expected in real world use, and are sufficient to inform the safety of Dexilant 30 mg daily for use in the treatment of sGERD in pediatric patients 12 -17 years of age.

For study 207, 62 patients were enrolled and started treatment in the open label phase of the trial, receiving 60 mg Dexilant daily for 8 weeks. The mean exposure 55 days (±9 days). Similar to study 206, patients were overall compliant as 29/ 62 (47%) patients took ≥ 57 doses, and 29/62 (47%) patients took their dose for 43-56 days out of the 8 week treatment period. This represents good compliance and the safety data from this trial are adequate to conclude that treatment with Dexilant short term over 8 weeks for healing of EE is safe and well tolerated.

Fifty eight of the sixty-two (94%) patients completed the open label phase. Of the 58 patients who completed the open-label treatment phase, 7 patients did not demonstrate healing and were ineligible for continuation into the double-blind maintenance phase, and 51 patients were eligible to continue. Of the 51 patients who were eligible to continue, 38/51 (75%) patients completed the full 16 week maintenance of healing phase. Compliance with the medication during the maintenance phase was also very good. Patients were exposed to the drug for a mean of 113 days in the treatment group and 102 days in the placebo group. The majority of patients in both placebo and treatment groups had nearly perfect (>113 days) or very good (85-112 days) compliance. Thus this reviewer concludes that the exposure of pediatric patients to dexlansoprazole in both phases of this study was sufficient to inform the safety of dexlansoprazole for the treatment of EE and maintenance of healing of EE in pediatric patients aged 12 to 17 years.

Premature discontinuations occurred in both placebo and treatment and were numerically similar (6 patients in placebo and 7 patients in treatment group) during the maintenance phase of the trial. Reasons for discontinuation are discussed in detail below in Section 7.3.3.

7.2.2 Explorations for Dose Response

Given available PK data suggesting that exposures for adolescents are very similar to those of adults, the applicant used the approved adult doses for both of the clinical trials. Patients received one dose (30mg daily) during study 206. Refer to section 6.1.8 for further discussion of the justification of the single dose design. In study 207, all patients received a standard dose for healing of EE (60 mg daily) during the initial 8 weeks. In the subsequent 16 weeks, they were randomized to receive either 30 mg daily (approved adult dose for maintenance of healing) or placebo. There was no additional dose-finding performed during either of these trials.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Routine testing was performed during both trials, including physical examination and measurement of vital signs, clinical laboratory tests at baseline and at conclusion of treatment, and ECG done at baseline and at conclusion of treatment. The list of laboratory tests obtained is provided in the Appendix, Table 30. Chemistry, hematology, and urine analysis tests were processed at a central laboratory.

7.2.5 Metabolic, Clearance, and Interaction Workup

Genetic testing was performed for all patients (unless prohibited by local law) for CYP2C19 genotype to determine the metabolizer status.

The majority of patients were extensive metabolizers of the drug. Data on the breakdown of metabolizer status in each study is presented below in Table 13.

Table 13: CYP2C19 Metabolizer Status

Metabolizer Status	Study 206 N=104 n (%)	Study 207 OL safety N=62 n (%)	Study 207 DB Treatment (30mg dex) N=25	Study 207 DB Placebo N=26
Extensive	73 (70)	48 (77)	20 (80)	22 (85)
Intermediate	27 (26)	9 (15)	5 (20)	3 (12)
Poor	2 (2)	2 (3)	0	1 (4)

(source: reviewer's table, created from data submitted in applicant's response to information request, received February 9, 2016, in Appendix A.)

The majority of patients were extensive metabolizers. The sample size of poor metabolizers is too small to draw meaningful conclusions about any potential

relationship between metabolizer status and adverse events. Refer to clinical pharmacology review by Dr. Shen Li for further discussion.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Patients in these trials were screened for known AEs associated with this drug class, including elevation of liver enzymes, hypomagnesemia, vitamin B12 deficiency, clostridium difficile colitis, and fractures.[17] These adverse events of interest were not identified in this submission, with the exception of one wrist fracture. Additional clinical information was requested from the applicant in an information request. This fracture occurred in a patient (7027-007) with no prior exposure to PPIs. The patient received a total of 52 days treatment with dexlansoprazole during the open label phase, and was later randomized to placebo. This fracture was assessed as mild, and resolved with conservative treatment. No bone density information was available, but given the limited exposure to dexlansoprazole of 52 days, and no history of prior exposure to PPIs, this reviewer considers this to be unlikely related to treatment The literature supports an association between long term PPI use and fractures in adults, but data to support that risk in children remains limited.[18]

Overall, this reviewer did not identify any new safety signals in the data submitted in this efficacy supplement.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during either study.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events were defined in the protocol, and were consistent with standard definitions as specified in §312.32(a). In addition, the applicant included a list of "Takeda Medically Significant Adverse Events" that were considered serious adverse events (see Appendix, Table 31).

No serious adverse events (SAE) occurred during study 206.

17 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#labelinfo
18 Freedberg DE, Haynes K, Denburg MR, et al. Use of proton pump inhibitors is associated with fractures in young adults: a population-based study. Osteoporos Int. 2015 Oct;26(10):2501-7.

In study 207, 5 SAEs were reported. One SAE (7043-003) (substance abuse) occurred during the open label phase. The remaining 4 events occurred during the double-blind maintenance portion of the trial and are summarized in Table 14 below. Further details and reviewer's assessment of causality are provided below.

Table 14: Treatment Emergent SAEs in Study 207, double blind phase

Event	**Treatment (30mg dexlansorpazole) N=25 n (%)**	**Placebo N=26 n (%)**
Intentional overdose (multiple substances)	0	1 (4%)
Worsening of underlying EE / lack of efficacy	1 (4%)	0
Seizure like episodes	1 (4%)	0
Influenza H1N1 Infection	0	1 (4%)

(source: reviewer's table, created from data provided in clinical study report for study 207, in appendix 16.2.7.3, and related eCRFs included in sNDA 22287 submission, received 9/30/15)

In the opinion of this reviewer, only one of these SAEs is potentially related to study drug use. The seizure like episodes are considered to be possibly related to study drug, in the opinion of this reviewer, given that convulsions are described in the approved product label and the temporal relationship of the events to the initiation of the study drug. This event is described below in more detail along with a summary of the other SAEs.

Patient # 7058-017 had a diagnosis of cognitive function deterioration prior to enrollment. His prior evaluation included MRI of the brain, EEG, lumbar puncture, and metabolic and lysosomal testing which all were negative, and the cause of the cognitive function deterioration remained unknown. This patient experienced 4 episodes of seizure-like movements during the trial, which were associated with headache and all of which occurred shortly after awakening. The patient underwent additional evaluation which included a sleep deprived EEG, which did not confirm seizure disorder, and was scheduled for MRI and MRI-angiography in follow-up (results not available). An etiology for the seizure-like events was not found and seizure like episodes did not recur. Given the inconclusive clinical evaluation, and the temporal relationship between the events and initiation of study drug, this reviewer concludes that a causal relationship is possible. Convulsions are listed in the approved product labelling as an adverse event noted during clinical trials in the adult population. Therefore, this reviewer concludes that changes to the label are not necessary based on this one report.

Patient #7043-003 was hospitalized twice during the trial for two separate SAEs, both due to intentional ingestion of substances other than the study drug. One ingestion was

reported to be the use of a street drug, ecstasy (which occurred during the open label phase), and the second involved deliberate overdose of multiple medications which did not include Dexilant. The patient had discontinued study drug prior to this event occurring. This reviewer agrees with the applicant's assessment that the events leading to hospitalization in both cases were unlikely to be related to the study drug.

Patient # 7056-005 was hospitalized due to worsening of abdominal pain. Endoscopic evaluation confirmed a worsening of previously known erosive esophagitis. This event reflects a lack of efficacy since erosive esophagitis describes the underlying disease, rather than an adverse reaction related to the study drug.

Patient # 7037-005 developed vomiting and subsequent dehydration, and tested positive for Influenza virus. Since the reported events of vomiting and dehydration can be ascribed to the viral infection, this reviewer agrees with the applicant's assessment that the vomiting and dehydration are likely related to Influenza and likely unrelated to the study drug.

Overall review of the SAEs did not identify any new or unexpected events would warrant changes or additions to the product labelling at this time.

7.3.3 Dropouts and/or Discontinuations

Study 206
Two patients discontinued the study medication prematurely for the following reasons:

- Patient 7036-004: Ongoing symptoms of GERD.
- Patient 7036-008: Dizziness rated as moderate in severity and possibly related to study drug. This symptom was resolving at the time of evaluation. This patient resumed treatment with ranitidine and omeprazole, both excluded medications, prior to end of study. Therefore, the patient was required to discontinue from the study.

Ongoing GERD is likely related to lack of efficacy, rather than an AE related to the treatment. Dizziness is a common complaint, and may be related to study drug. The patient was improving after discontinuation, and dizziness is listed as an adverse event in the current product labelling. Therefore, no changes in labelling are recommended based on these two reports.

Study 207
Open Label Healing Phase:
Of the 63 patients enrolled, 1 patient (7037-006) did not take any doses of the study medication, discontinued visits due to pretreatment events (worsening of pain from ovarian cyst, abnormal appendix), and ultimately was withdrawn from the trial due to noncompliance. Of the 62 patients who started treatment with the study drug, 58 patients completed the 4-week open-label treatment. There were 4 patients who

discontinued early for the following reasons: (1) adverse event (urticaria), (1) lost to follow up, (1) voluntary withdrawal (not improving on treatment), and (1) major protocol violation (patient was found to have eosinophilic esophagitis).

Double-Blind Maintenance Phase:
After endoscopic evaluation at the conclusion of the open-label phase, 51/58 (88%) demonstrated documented healing of EE, and were eligible to be randomized into the double-blind maintenance phase of the trial. Of the 51 patients, 13 patients discontinued prematurely (6 in placebo, 7 in treatment arm). Refer to Table 9, discussed in section 6.2.3 above for more details.

Upon review of the totality of data, the withdrawals and discontinuations related to lack of efficacy overall included 5/26 (19%) patients in placebo group, and 2/25 (8%) patients in treatment group. This includes 1 patient in the placebo group who discontinued because "GERD symptoms returned" and one patient in Dexilant treatment group who discontinued because of an "Adverse event of EE".

While this reviewer acknowledges that it is difficult to draw definite conclusions based on the small number of patients, the discontinuations due to lack of efficacy were numerically greater in the placebo group as compared to the Dexilant group. This observation may support the clinical benefit of treatment with dexlansoprazole for the maintenance of healing of EE.

7.3.4 Significant Adverse Events

The majority of adverse events reported were mild to moderate in severity. There were 5 AEs that were rated as "severe" reported during the two clinical trials.

In study 206, patient 703-6004 experienced an AE of abdominal pain that was reported as severe in intensity on study day 11. The pain resolved without change in dose/medication. This patient then discontinued prematurely (study day 15) due to symptoms of GERD. Abdominal pain is often associated with GERD in pediatric patients; therefore, this event may represent a lack of efficacy, rather than an adverse reaction caused by the medication.

In study 207, there were a total of 5 events rated as "severe" in intensity. Table 15 below summarizes the severe treatment emergent adverse events, by dose.

Table 15: Severe TEAE, by treatment arm, study 207

"Severe" TEAE	Open-Label Phase	Double-Blind Maintenance Phase	
	Dexilant 60mg N = 62 n (%)	Placebo N = 26 n (%)	Dexilant (30 mg) N = 25 n (%)
Erosive Esophagitis	1 (2%)	0	1 (4%)
Intentional Poisoning[1]	1 (2%)	0	0
Shoulder Dislocation	0	1 (4%)	0

[1] *Two occurrences of intentional poisoning occurred for this patient, one in open label phase, and a second similar occurrence after discontinuation of study drug. The patient ingested illegal drugs, including ecstasy, and other multiple medications but not including dexlansoprazole.*
(source: reviewer's analysis from data provided in applicant's sNDA22287 submission, received 9/30/15, end of text tables from clinical study report for study 207, Table 16.2.7.1)

Both cases of erosive esophagitis occurred in patients who were receiving treatment with the study drug (one event occurred during the open-label treatment phase and one event occurred during the double-blind maintenance phase; the patient was receiving dexlansoprazole 30 mg). Both events are likely reflective of lack of efficacy and should be considered as treatment failures.
The other events (i.e., drug ingestion and shoulder dislocation) are not related to the study medication. Refer to section 7.3.2 for discussion of SAEs for patient 7043-003 (intentional poisoning).

7.3.5 Submission Specific Primary Safety Concerns

The warnings and precautions found in the approved product labelling for adults list events of interest for this product including fractures, hypomagnesemia, and clostridium difficile infection.[19] One wrist fracture occurred during study 207 (refer to section 7.2.6 for further details), and no fractures were reported during study 206, though the trial duration of study 206 was short (4 weeks). There were no cases of hypomagnesemia or clostridium difficile in either study. There were 2 cases of "gastroenteritis" reported which were not further defined as viral or bacterial. Additional information provided by Takeda in response to an Information Request from the Division clarified that both events were short duration, mild cases and in the opinion of this reviewer do not appear to be consistent with Clostridium difficile infection.

One potential safety concern noted by this reviewer is the development of hypernatremia during the trials. This is discussed in greater detail below.

19 Approved product labelling for Dexilant, updated 12/16/2015, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022287s018lbl.pdf

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

This section will discuss treatment emergent adverse events (TEAEs) by study, and as pooled data.

Study 206:
Overall, 36/104 (35%) patients experienced at least one TEAE during study 206. The majority were mild and self- limited. Table 16 below summarizes the commonly seen treatment emergent adverse events which occurred during study 206.

Table 16: TEAEs seen in 2 or more patients (Study 206)

Adverse Event	**30 mg Dexilant N=104 n (%)**
Any TEAE	36 (35%)
Abdominal pain[1]	9 (9%)
Diarrhea	7 (7%)
Headache	7 (7%)
Vomiting	3 (3%)
Herpes Simplex[1]	3 (3%)
Bronchitis	2 (2%)
Dizziness	2 (2%)
GERD	2 (2%)
Increased appetite	2 (2%)
Influenza	2 (2%)
Nasopharyngitis	2 (2%)
Oropharyngeal pain	2 (2%)

[1]*The reviewer combined abdominal discomfort (1), abdominal pain upper (4), abdominal pain lower (1) into "abdominal pain" and with oral herpes (2) with "herpes simplex virus".*
(source: reviewer's analysis, using applicant's submitted data in NDA22287, dated 9/30/2015, ADAE dataset for study 206)

The most commonly reported adverse events (AEs), seen in ≥5% of patients were abdominal pain, diarrhea, and headache. Abdominal pain and diarrhea were also among the most commonly reported AEs seen in the adult studies and are described in in the current labelling. Abdominal pain is also a common complaint of children with GERD, and may represent ongoing symptoms of the underlying condition, rather than an adverse reaction due to the study drug. Headache was not a commonly reported AE in the adult studies, and may be treatment related, and should be included in the product labelling. Overall the AE profile was similar between adults and pediatric patients 12 – 17 years of age.

Study 207:
The adverse event profile was similar in study 207, and included a placebo arm for comparison during the double blind phase. Table 17 and Table 18 below describe the commonly seen treatment-emergent adverse events, observed in 2 or more patients in either phase of the trial. In the open label phase, 38/62 (61%) patients experienced at least one TEAE. The majority were mild to moderate in severity, and the overall profile was similar to that reported in adults.

Table 17: TEAE seen in 2 or more patients, Study 207, Open Label Phase

Adverse Event	**60 mg Dexilant N=62 n (%)**
Any TEAE	38 (61%)
Headache	8 (13%)
Oropharyngeal Pain	5 (8%)
Nasopharyngitis	4 (7%)
Abdominal pain[1]	4 (7%)
Diarrhea	4 (7%)
Pharyngitis	3 (5%)
Respiratory Tract Infection[1]	3 (5%)
Urticaria	2 (3%)
Vomiting	2 (3%)

[1] *upper respiratory infection (2) is combined with respiratory tract infection (1) and abdominal pain upper (1) with abdominal pain (3).*
(source: reviewer's table, created using applicant's data provided in NDA22872 submission, dated 9/30/15, ADAE dataset for study 207)

One notable difference between adolescents and adults is the presence of headache as a common AE. This AE is unique to patients 12 to 17 years of age, and should be included in the product labelling for pediatric patients given that headache is not described as a common adverse event in the label for the adult patients.

Oropharyngeal pain may be related to study drug, but in the opinion of this reviewer, is more likely a symptom of underlying EE. Similarly, abdominal pain is a frequent complaint of pediatric and adolescent patients with acid mediated disease, and so may represent either a drug related AE, or may be a symptom of underlying disease.

Table 18: TEAE seen in 2 or more patients (greater frequency than placebo), by treatment arm - Study 207, Double Blind Phase

	30 mg Dexilant N=25 n (%)	Placebo N=26 n (%)
Any TEAE	18 (72%)	16 (62%)
Headache	6 (24%)	4 (15%)
Pharyngitis	3 (12%)	0
Sinusitis	3 (12%)	0
Insomnia	2 (8%)	0
Respiratory tract infection	2 (8%)	0
Bronchitis	2 (8%)	1 (4%)

(source: reviewer's analysis, created using applicant's data provided in sNDA22287, dated 9/30/2015, ADAE dataset for study 207)

Thirty four of 51 (67%) patients experienced at least one TEAE during the double blind portion of study 207. Again the reviewer notes that headache is the most common reported TEAE. Although it occurs often in placebo as well as in the treatment group, the overall frequency of headache among adolescent patients in both studies suggests that this may be an important adverse event that is specific to this pediatric population 12 to 17 years of age. The infectious TEAEs reported including pharyngitis, sinusitis, and respiratory tract infections were seen more often in those on treatment than on placebo, and may represent a related treatment AE. However, upper respiratory tract infections are common in children and adolescents, particularly during certain seasons, and this is most likely unrelated to treatment. Dexlansoprazole or other drugs in this class do not have any known immune suppressant action that would predispose to this type of infection.

In addition to the TEAEs seen above, abdominal pain was frequently reported in all groups, though with greatest frequency in the placebo group, which may suggest that abdominal pain is a symptom of underlying disease rather than a treatment related AE.

Pooled Adverse Event Summary:

Adverse event reports were combined to assess the overall most common TEAEs seen across both studies in the 12 to 17 year age group. The results were similar to the results when the data were analyzed by individual study, and are overall consistent with the AE profile reported in the adult trials. Headache, abdominal pain, diarrhea, and nasopharyngitis were the most commonly reported TEAEs. Table 19 below summarizes the most common TEAEs seen in ≥5% of patients across both studies.

Table 19: Most Common TEAEs Seen in ≥5% of patients across both studies

TEAE	N=166 n (%)
Headache	20 (12)
Abdominal Pain	17 (10)
Nasopharyngitis	16 (10)
Diarrhea	11 (7)
Oropharyngeal Pain	8 (5)

(Source: Reviewer's analysis of data provided in ADAE datasets for study 206 and study 207).

The reported cases of numbers of adverse events in this pooled analysis differ slightly from those provided by the applicant in Table L2.1 (submitted with draft labelling, received June 4, 2016). The main difference is that this reviewer tabulated all treatment emergent AEs occurring across both studies, regardless of dose/treatment arm. In the applicant's analysis, events were excluded if they occurred in the placebo arm, or in the post-maintenance treatment follow-up period as patients were not receiving treatment during the follow up period. However, this reviewer determined that these groups may have treatment related events that should be accounted for (for example, if an event occurred in a patient on placebo, less than 30 days after last open label dose, that event is still within the timeframe for "treatment emergent" from the open label dose). Additionally, this reviewer included "abdominal discomfort" with abdominal pain. These differences produced minor differences in the AE counts for abdominal pain when compared with the applicant's provided data. However, overall the most frequently occurring TEAEs occurring in ≥5% of patients are the same.

The commonly reported adverse events across the pooled population are similar to the AE profile discussed under the individual studies above, and these data should be included in the labelling for patients aged 12 to 17 years.

7.4.2 Laboratory Findings:

Overall the changes in laboratory parameters were small fluctuations from baseline values, and were not clinically meaningful. This reviewer attempted to identify laboratory abnormalities currently described in the label, identified from the adult patient population, including hypomagnesemia and vitamin B12 deficiency, decreased platelet count, and elevations in liver enzymes, bilirubin, potassium, calcium, and creatinine. No clinically meaningful changes in any of these parameters were identified. Laboratory findings will be summarized by type, and were assessed separately for each study.

Hematology Findings:

Study 206:
There were no significant abnormalities or changes in the mean hematology parameters from baseline to week 4. Shifts occurred in individual patients but were generally small and not clinically meaningful.

The applicant identified cut-off values for laboratory assessments that were considered as critically abnormal. This reviewer concludes that the values selected by the applicant appear appropriate to identify potentially clinically significant changes in the major hematology parameters (refer to appendix, Table 32 for specific cut-offs). There were no patients who developed changes in hemoglobin/hematocrit, platelet count, white blood cell count, or red blood cell count that were flagged as critically abnormal.

Shifts in laboratory values for individual patients were reviewed. There were moderate changes from baseline in the absolute monocyte count (14 patients, measured values from 0.06-0.29 x10^3 cells/uL, normal range 0.3-1.3 x10^3 cells/uL) and absolute white blood cell count (20 patients, measured values ranged from 2.7 to 4.8 x10^3 cells/uL, normal range 4.9 to 15.5 x10^3 cells/uL). Overall the shifts were not clinically meaningful. This reviewer notes that isolated decrease in monocytes are unlikely to have clinical relevance. The decreased white blood cell counts were generally mild. Associated absolute neutrophil counts also were assessed by the reviewer, as significant decrease in neutrophil count may predispose patients to severe bacterial infections. Only one patient (701-7003) developed a significantly low count of 540 cells/uL. An information request was sent to the applicant to obtain further clinical information, which is summarized here. This subject had neutropenia and leukopenia (to a lesser degree) during the screening period, prior to study drug administration. Additionally the subject is African American, an ethnic group predisposed to benign familial neutropenia. As the investigator did not find the result to be clinically significant, no follow-up measurements were obtained. This patient had no reported AEs during the study. The relationship between this low neutrophil count and the study drug is unclear. Dexilant was not reported to cause bone marrow suppression or neutropenia in controlled clinical trials in adults.[20] In this reviewer's opinion, the most likely explanation for transient neutropenia in an otherwise healthy adolescent is a recent viral infection. Based on the mechanism of action of Dexilant and the available data in large clinical studies in adults, it is unlikely that this event was related to treatment. Of note, no patients developed significant anemia or thrombocytopenia during the 4 week study.

20 Approved product label for Dexilant, updated 12/16/2015, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022287s018lbl.pdf.

Study 207:
There were no meaningful abnormalities or changes in the mean hematology parameters from baseline to week 4. Shifts occurred in individual patients but were generally small and of no major clinical consequence.

There were no clinically meaningful changes in white cell count, platelet count, or anemia, as flagged by the critical flags. In addition, all shifts outside the normal range were reviewed and there were no clinically meaningful trends noted.

Chemistry:

Study 206:
There were no clinically meaningful changes in the mean values for any chemistry values, with the exception of serum gastrin.

Individual patient results were evaluated for critically abnormal values, using the applicant provided cutoffs, with the following modifications. This reviewer applied more stringent criteria for potassium and creatinine, to ensure no clinically relevant changes were overlooked, as discussed below. Refer to appendix, Table 33 for further details.

Serum gastrin:
Mean serum gastrin levels rose from a baseline of 31 pg/ml to 71 pg/ml at week 4. Additional levels were not collected during the post treatment period. This rise in serum gastrin is expected given the mechanism of action of the drug, and is similar to changes seen in the adult trials.

Sodium:
Five patients developed hypernatremia with sodium >150mEq/L. Reported values ranged from 151-154 (individual patients had change of between 5- 10 mEq/L from baseline). The review team issued an Information Request to obtain additional information to better evaluate whether the events of hypernatremia were clinically relevant. No adverse events were reported for any of the patients with hypernatremia during the trial. It is noted that for 2/5 patients, serum sodium was also elevated at screening, and therefore is less likely related to treatment. For one patient, the serum sodium remained high 18 days after last dose (early discontinuation due to GI side effects) suggesting that hypernatremia was not related to treatment, given the short half-life of the medication. The remaining 2 patients had moderate elevation of sodium while on treatment. No significant AEs were reported and no further follow up information is available. Of note, elevations in serum sodium also occurred in study 207, but in similar numbers of patients between the placebo and dexlansoprazole groups (discussed in more detail below). Based on the available information, this reviewer concludes that these changes are unlikely to represent an adverse reaction that is related to treatment with dexlansoprazole.

Creatinine
Creatinine values were found to be elevated above 1 mg/dL in 8 patients during the trial, and were not considered as clinically meaningful. The mean baseline values for the 8 patients ranged from 0.9 mg/dL to 1.1 mg/dL and were slightly elevated at week 4, 1.0 mg/dL to 1.2 mg/dL, with mean change of 0.2 mg/dL from baseline. This reviewer does not consider the changes to be clinically significant or indicative of a significant change in renal function.

Uric Acid:
Six patients developed mildly elevated uric acid levels (ranging from 5.8 to 8.8 mg/dL). Baseline uric acid value was 4.9 ± 1.3 mg/dL, and week 4 mean value was 4.8 ± 1.2 mg/dL. No associated reports of renal stones or gout occurred to suggest a clinical consequence of the individual patient shifts.

Bicarbonate:
Sixteen patients shifted from normal baseline to low values of bicarbonate. However, the values (mean 19 mEq/L, range 17-20 mEq/L) were all minimally below the normal cutoff (19-21 mEq/L), and this reviewer determined that bicarbonate levels in this range are unlikely are unlikely to cause clinical sequelae. The mean value was 20 ± 2 mEq/L at baseline, and was 20 ± 2 mEq/L at week 4 (mean change from baseline of 0.1 meq/L).

Other electrolytes (Magnesium, Calcium, Phosphorus, Glucose):
No significant abnormalities occurred in serum magnesium or calcium. There were no cases of hypophosphatemia. There were minimal shifts from baseline in phosphorous, but they were mild and not clinically concerning. The mean phosphorus level was 4.3 ± 0.6 mg/dL at baseline, and at week 4 the mean value was 4.3 ± 0.6 mg/dL. Mean serum glucose was 91 ±10 mg/dL at baseline, and was 90 ± 8 mg/dL at week 4.

Urine Analysis:
One patient developed proteinuria 2+ or greater, who was negative at baseline. Nine patients who were negative for hematuria at baseline had detectable hematuria on urine analysis at week four, ranging from trace to 3+. However, given there were no reported cases of renal insufficiency, and none of these patients had concomitant proteinuria, the noted hematuria is more likely due to contamination, menses, or poor collection technique, rather than a manifestation of renal disease (all of these patients were female).

Study 207:
Overall there were no notable shifts in the mean from baseline in any of the chemistry parameters, with the exception of serum gastrin.

Serum gastrin: Mean serum gastrin levels increased from baseline to week eight (during the open label phase) from 21 pg/ml to 76 pg/ml. In the double-blind phase, the patients

in the placebo arm returned to baseline within eight weeks and then stayed in the normal range through the conclusion of the study. Patients in the treatment arm (receiving 30mg daily) had levels that decreased slightly (mean of 82 at the start of the open label phase, to mean of 60 at week 24). The levels remained significantly above pre-treatment levels. The changes seen in this study reflect what is known about the mechanism of action of the drug, and show that there is a fairly rapid return to baseline once treatment is discontinued.

Chemistry:
Patients were evaluated for critically abnormal values with the same criteria as described above (see Appendix, Table 33). Details are provided below, but overall the shifts in individual patients were relatively small, and no concerning trends were identified.

Hypernatremia: Similar to study 206, 5 patients developed hypernatremia in the open label phase. Reported values at week 4 (4 cases) or week 8 (1 case) ranged from 151-153 mEq/L with a mean change from baseline of 9 mEq/L (range 3 to 13 mEq/L). However, in the double blind phase, 4 patients developed abnormal elevations of sodium. Three of the four patients were receiving placebo. The values during the double blind phase (for the patients receiving placebo) ranged from 151-159 mEq/L with a mean change from baseline of 10 mEq/L (range 5-15 mEq/L). The one patient receiving study drug had a lesser elevation to 155 mEq/L, which returned to his/her baseline during the remaining time he received treatment.

Noting that elevations occurred in a similar number of patients while on placebo, compared with those receiving open label treatment, this reviewer concludes that these changes are unlikely to be attributable to the study drug. Additionally, hypernatremia was not observed in the adult clinical trials.

Creatinine: Only minimal shifts from baseline were noted in individual patients, occurring with similar frequency in both the treatment and placebo groups, and are not clinically concerning to this reviewer. The mean baseline value was 0.8 ± 0.2 mg/dL and week 24 values were 0.8 ±0.1 mg/dL in the placebo group, and 0.8 ± 0.2 mg/dL in the treatment group.

Calcium:
No cases of hypocalcemia occurred during the study. There were small changes from normal to elevated calcium levels in a small number of patients, but the overall changes were small and unlikely to carry clinical consequence. The mean value was 9.9 ±0.4 mg/dL at baseline, and the week 24 values were 9.9 ± 0.4 mg/dL in the placebo group, and 10 ± 0.5 mg/dL in the treatment group.

Other electrolytes:
No hypomagnesemia or hypoglycemia occurred during study 207. There were minimal changes from baseline in the glucose of a small number of patients in both the treatment and placebo groups, but changes were small and unlikely to be of clinical significance. Mean serum glucose was 90 ± 7 mg/dL at baseline, and the week 24 values were 89 ± 8 mg/dL in the placebo group, and 91 ± 11 in the treatment group. Mean changes from baseline were 8-10.

Vitamins of Interest

Vitamin B12
Table 20 below summarizes the changes in vitamin B12 levels throughout both studies. Of note, values beyond week 4 are not included for study 206 since this study duration was 4 weeks.

Table 20: Vitamin B12 Levels over time (Study 206 and 207)

	Study 206 30mg Dex	**Study 207** 60 Dex (baseline – Week 8) then 30mg Dex
Baseline (pg/mL)		
Mean ± SD	451 ± 153	473 ± 212
Median	430	418
Range	(171, 926)	(219, 1380)
Week 4 (pg/mL)		
Mean ± SD	449 ± 143	468 ± 214
Median	444	417
Range	(175, 917)	(205, 1571)
Week 8 (pg/mL)		
Mean ± SD		457 ± 18
Median		418
Range		(200,122)
Week 24 (Placebo) (pg/mL)		
Mean ± SD		541 ± 250
Median		459
Range		(250, 1220)
Week 24 (treatment) (pg/mL)		
Mean ± SD		419 ± 134
Median		376
Range		(236, 703)

(source: reviewer's analysis, created from data in applicant's sNDA 22287 submission, dated 9/30/15, data from Tables 15.3.4.1.3.4.1, 15.3.4.1.3.4.2, 15.3.4.1.3.4 included in clinical study reports for studies 206 and 207)

This reviewer notes no meaningful change from baseline levels of vitamin B12 to week 4 or 8 of treatment. However, it is notable that by week 24, the levels rose nearly 100 pg/mL on average in patients who stopped treatment at week 8 (i.e., were randomized to placebo), vs those who continued on treatment to week 24. Given that the normal range for vitamin B12 is very wide (normal 211-911 pg/mL) and the relatively small number of patients who continued into the maintenance phase, the data are limited to draw a definitive conclusion about the possible effect of 24 weeks of treatment on B12 levels. The concern of B12 deficiency occurring in long term use of PPIs is already reflected in the label.

Vitamin D (25OH Vit D)

Table 21 below summarizes baseline and treatment values of vitamin D. Of note, values beyond week 4 are not included for study 206 since this study duration was 4 weeks.

Table 21: Vitamin D (25-OH Vitamin D) levels (Study 206 and 207)

	Study 206 30mg Dex	**Study 207** 60 Dex (baseline – Week 8) then 30mg Dex
Baseline (pg/mL)		
Mean ± SD	25 ± 10	22 ± 8
Median	24	21
Range	(4, 63)	(8, 48)
Week 4 (pg/mL)		
Mean ± SD	25 ± 10	21 ± 7
Median	24	21
Range	(6, 57)	(8, 40)
Week 8 (pg/mL)		
Mean ± SD		21 ± 8
Median		21
Range		(9, 35)
Week 24 (Placebo) (pg/mL)		
Mean ± SD		24 ± 11
Median		20
Range		(11, 46)
Week 24 (treatment) (pg/mL)		
Mean ± SD		23 ±7
Median		23
Range		(11, 36)

(source: reviewer's analysis, created from applicant's sNDA22287 submission, received 9/30/15, data in Table 15.3.4.1.3.4.1,Table 15.3.4.1.3.4.2, Table 15.3.4.1.3.4 in clinical study reports for studies 206 and 207.)

No meaningful changes in mean vitamin D levels occurred over the course of either trial.

7.4.3 Vital Signs

Study 206:
Vital signs including height, weight, blood pressure, temperature, and heart rate were measured at baseline and week 4. Mean changes in vital signs were minimal overall. There was only one patient who developed hypertension with systolic blood pressure (SBP) >140, who reported an AE of headache (mild), which may possibly be related. Fifteen patients developed systolic blood pressure <100 during the treatment period. For 6 of those patients, this represented a decrease in more than 10 mmHg from baseline. The reported AEs for these patients were unlikely to be related to the decreased blood pressure (such as food allergy, abdominal or oropharyngeal pain, headache or bronchitis). There were no patients with decreased BP who reported dizziness, lightheadedness, or syncope.

Study 207:
One patient developed hypertension (SBP>140) in the open label phase. Three patients on treatment developed mild hypertension (SBP ranging 141-148) during the open label phase, and two patients on placebo had similar mild elevations (SBP 141). Given that nearly equal numbers of patients had these minimal changes in both groups, it is less likely that hypertension is attributable to the study drug. No diastolic blood pressures greater than 100mm Hg were reported. Seven patients developed systolic blood pressure <100 in the open label phase. The changes were relatively small and all of these patients started with low blood pressures (baseline 86-111, measured values 80-99, with a mean change of -5). Similar small changes occurred in the double blind phase, and were equally split among patients receiving placebo vs treatment (5 in placebo, 4 in treatment). These changes were most likely related to individuals' day to day variability.

There were four patients who developed bradycardia of <50 beats per minute during the study: 2 occurred in patients on placebo, and 2 in patients on treatment. The range of heart rates for these patients was 43-49 beats per minute (change of -8 to -24 bpm). None of these patients reported adverse events that could be attributable to decreased heart rate such as syncope, presyncope, or dizziness.

Overall the changes in vital signs across both studies were fairly minimal and not clinically concerning.

7.4.4 Electrocardiograms (ECGs)

Study 206:
There were no ECGs recorded as abnormal and clinically significant during the study.

Study 207:
One patient (7037-001) had reported change in ECG from abnormal (not significant) to abnormal (clinically significant). Additional information was requested from the applicant, and was received in the response to information request dated 3/10/2016. Patient 7037-001 received open label treatment for the full 8 weeks, and had a normal ECG done at the conclusion of the open label period. He subsequently was assigned to placebo for the double-blind period, and the abnormal ECG in question was done on study day 162, while in the placebo group. The ECG was read as "left atrial abnormality, nonspecific ST-T changes, and early repolarization." The patient was referred for thorough cardiology evaluation. The results of the cardiology evaluation concluded that although there was an abnormality noted on the ECG in question, the patient had a normal cardiac examination, was asymptomatic, and was to be treated as a normal, healthy child without restrictions. Based on this additional information provided, this reviewer concludes that this is not a significant concerning AE.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

There were no immunogenicity concerns associated with this product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Patients received 30mg daily dexlansoprazole in study 206, and 60mg daily dexlansoprazole during the open label portion of study 207, then 30mg vs placebo in the double blind phase.

The commonly observed adverse events were fairly similar in frequency and severity between the two trials, and were generally mild. It is not useful to compare the overall incidence of TEAEs in one dose group compared with the other, because the patients in study 206 had a different underlying condition than those in study 207. Within study 207, the percentage of patients experiencing at least one TEAE was greater on the 30mg dose (DB) (18/25, 72%) than at the 60mg dose (OL) (38/62, 61%), though the patient numbers are small. Overall, the data provided from these two different trials do not suggest a higher incidence of AEs with use of the higher 60mg dose.

7.5.2 Time Dependency for Adverse Events

Time dependency was not assessed for study 206, as the treatment duration was only 4 weeks.

In study 207, the rate of AEs increased slightly as the trial progressed. In the initial, open label phase, 61% of patients reported experiencing at least one AE. That number increased to 72% during the double blind phase for patients on treatment. Those receiving placebo in the second phase had a rate of AEs very similar to the initial 8 weeks (62%).

Given the very small numbers of patients in the second portion of the trial (25 patients on treatment in double blind portion), it is not possible to conclude from this small patient population whether the frequency of these AEs represent a meaningful difference relating to the dose or exposure duration.

7.5.3 Drug-Demographic Interactions

Because the study was already conducted in a well-defined, narrow age range of adolescent patients 12-17 years of age, no additional analysis was done by age group. Similarly, as greater than 95% of the enrolled patients where white, it is not meaningful to analyze safety data by race.

Adverse events were evaluated by sex for both studies. In study 206, abdominal pain, headache, and diarrhea were among the most common AEs seen, and were noted more frequently in females as compared with males. Table 22 below summarizes the most common TEAEs by sex. Given the small numbers, no meaningful difference in adverse events by sex is detected.

Table 22: Most Common AE by Sex (Study 206)

Event	Female N = 73 females n (%)	Male N= 31 males n (%)
At least 1 TEAE	28 (38)	9 (29)
Abdominal Pain	6 (14)	3 (10)
Diarrhea	5 (7)	2 (7)
Headache	6 (8)	1 (3)
HSV	3 (4)	0
Vomiting	3 (4)	0
Influenza	0	2 (7)
Dizziness	0	2 (7)
Bronchitis	0	2 (7)
Increased appetite	2 (3)	0

(source: reviewer's analysis, from data provided in applicant's NDA 22287submission, dated 9/30/15, ADAE dataset for study 206)

In study 207, the most common AEs are assessed by gender for both the open label and double blind phases. In the open label phase, the occurrence of at least one TEAE was similar in both sexes. The most commonly reported TEAEs by gender included nasopharyngitis, pharyngitis, and headaches in the female patients, and headache, oropharyngeal pain, diarrhea, and URI in the males. A summary of the TEAEs occurring 2 or more patients in either sex is summarized in Table 23 below.

Table 23: Most Common TEAE by Sex, Open Label Phase, (Study 207)

Event	Female Dose: 60mg dex N = 24 n (%)	Male Dose: 60mg dex N= 38 n (%)
At least 1 TEAE	15 (63)	23 (61)
Headache	2 (8)	6 (16)
Nasopharyngitis	4 (17)	0
Abdominal pain	2 (8)	2 (5)
Pharyngitis	3 (13)	1 (3)
Diarrhea	1 (4)	3 (8)
Oropharyngeal pain	1 (4)	4 (11)
Upper respiratory tract inf	0	3 (8)
Vomiting	0	2 (5)

(source: reviewer's analysis, from data provided in applicant's sNDA 22287 submission, dated 9/30/15, ADAE dataset for study 207)

Overall, the small patient numbers limit conclusions that can be drawn from these analyses concerning the role of gender on the AE profile of Dexilant in this population.

In the double blind phase, the patient numbers were very small in each group, when divided by treatment arm and sex. There were no meaningful trends noted based on sex. Table 25 below lists the most common TEAEs seen in the double blind phase of study 207 by sex.

Table 24: Most common TEAEs in DB phase, by Sex and Treatment Arm (Study 207)

Event	Female		Male	
	30mg dex N=11 n (%)	Placebo N=10 n (%)	30mg dex N=14 n (%)	Placebo N=16 n (%)
At least 1 TEAE	9 (82)	6 (60)	9 (64)	10 (63)
Headache	2 (18)	1 (10)	4 (29)	3 (19)
Insomnia	1 (9)	0	1 (7)	0
Abdominal pain	3 (27)	2 (20)	1 (7)	3 (19)
Pharyngitis	0	0	3 (21)	0
Sinusitis	0	0	3 (21)	0
Nasopharyngitis	1 (9)	1 (10)	2 (14)	3 (19)
Diarrhea	0	0	0	2 (13)
Pyrexia	0	0	0	2 (13)
EE	1 (9)	0	0	2 (13)
Gastroenteritis	0	0	0	2 (13)

(source: reviewer's analysis, created from data provided in applicant's sNDA 22287 submission, dated 9/30/15, ADAE dataset for study 207.)

7.5.4 Drug-Disease Interactions

No specific studies were done to assess drug-disease interactions in these studies.

7.5.5 Drug-Drug Interactions

No specific studies were done to assess drug-drug interactions in these studies.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No additional carcinogenicity studies were submitted with this supplement.

7.6.2 Human Reproduction and Pregnancy Data

No additional non-clinical studies were submitted with this supplement.

7.6.3 Pediatrics and Assessment of Effects on Growth

Effects on growth and development were not specifically studied in these trials. Study 206 was insufficient in duration (4 weeks) to draw conclusions about effects on growth. In study 207, the patients who continued into the maintenance phase were followed for 36 weeks total. Typically, a minimum of one year of follow-up data is required to make a meaningful assessment of changes in linear growth. The data provided including heights/weights in this study did not demonstrate any meaningful differences in growth based on assigned treatment group, within the 36 weeks of data available.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No specific information was provided regarding Dexilant in overdose with this submission.

Overdose:
The approved product labelling notes that multiple doses of Dexilant 120 mg or a single dose of Dexilant 300 mg did not result in death or other severe AEs (in adults). Some serious AEs of hypertension were noted at doses of 60mg twice daily given in adults. Dexilant is not expected to be removed from the circulation by hemodialysis.[21]

Withdrawal and Rebound:
At the conclusion of the double blind treatment period for study 207 (week 24-28) patients were followed for an additional 12 weeks, off treatment, to monitor for recurrence of symptoms or need to restart treatment. Only one patient had recurrence of symptoms which required re-initiation of treatment with PPI during this period, suggesting that the therapeutic effect of dexlansoprazole generally persisted during this time. Further, it is reassuring that no patients experienced a significant worsening immediately after stopping treatment, as “rebound acid production” is a theoretical concern when discontinuing use of a PPI. Refer to section 6.2.9 above.

21 Approved product labelling for Dexilant, updated 2/2/2016, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022287s020lbl.pdf

7.7 Additional Submissions / Safety Issues

A 120 day safety update was not submitted under this sNDA. The pediatric trials were complete and no additional data were available outside of the data provided in the submission. The applicant notes that no new non-clinical or clinical studies have been initiated since the submission of this supplement.

8 Postmarket Experience

Dexlansoprazole was first approved in the United States for use in adults in 2009. The postmarketing experience is described in the label, which was updated most recently in in December 2015 with the approval of Dexilant SoluTab. The following are the listed adverse events reported in the post-marketing data.

- Blood and Lymphatic System Disorders: autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura
- Ear and Labyrinth Disorders: deafness
- Eye Disorders: blurred vision
- Gastrointestinal Disorders: oral edema, pancreatitis
- General Disorders and Administration Site Conditions: facial edema
- Hepatobiliary Disorders: drug-induced hepatitis
- Immune System Disorders: anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal)
- Infections and Infestations: Clostridium difficile associated diarrhea
- Metabolism and Nutrition Disorders: hypomagnesemia, hyponatremia
- Musculoskeletal System Disorders: bone fracture
- Nervous System Disorders: cerebrovascular accident, transient ischemic attack
- Renal and Urinary Disorders: acute renal failure
- Respiratory, Thoracic and Mediastinal Disorders: pharyngeal edema, throat tightness
- Skin and Subcutaneous Tissue Disorders: generalized rash, leukocytoclastic vasculitis

None of these events occurred in a large proportion of patients during the pediatric clinical trials reviewed in this submission.

The last periodic safety update was submitted by Takeda on March 27, 2015 covering the reporting period from January 30, 2014 through January 29, 2015. Post-market

exposure during the reporting period is estimated at 673,002 patient years in North America.

During the reporting period label revisions were requested by FDA to address a contraindication and warning for acute interstitial nephritis, and a warning for vitamin B12 deficiency, as well as a drug interaction for mycophenolate mofetil. The revised label was approved December 19, 2014.

Additionally a revision was made in the reference safety information to clarify that caution should be used when administering HIV protease inhibitors in conjunction with dexlansoprazole.

No new safety signals were reported in this periodic safety update that are not currently described in the approved product label.

9 Appendices

9.1 Literature Review/References

Boccia G, Manguso F, Miele E, et al. Maintenance therapy for erosive esophagitis in children after healing by omeprazole: is it advisable? Am J Gastroenterol 2007; 102:1291-97

Fennerty M. Medical treatment of GERD in the managed care environment. *Semin Gast Dis* 8: 90-99; 1997.

Tolia V, Youssef N, Gilger M, et al. Esomeprazole for the treatment of erosive esophagitis in children: an international, multicenter, randomized parallel-group, double blind (for dose) study. BMC Pediatrics. 2010;10:41.

Saitoh T, Otsuka H, Kawasaki T, et al. Influences of CYP2C19 polymorphism on recurrence of reflux esophagitis during proton pump inhibitor maintenance therapy. Hepatogastroenterology. 2009.

Sherwood, MW, Melloni C, Jones WS, et al. Individual proton pump inhibitors and outcomes in patients with coronary artery disease on dual antiplatelet therapy: a systematic review. J Am Heart Assoc. 2015; 4:e002245. DOI 10.1161/JAHA.115.00245

Yamamoto E, Brito HS, Ogata SK, et al. High rate of clinical and endoscopic relapse after healing of erosive peptic esophagitis in children and adolescents. J Pediatr Gastroenterol Nutr. 2014 Nov; 59(5): 595-9.

9.2 Labeling Recommendations

The labeling negotiations were ongoing at the time this review was finalized. For final labeling agreements, see the approved product label for Dexilant and Dexilant SoluTab. This reviewer recommends the following revisions to the proposed label:

- Throughout the proposed label, the term (b) (4) was revised to read "pediatric patients 12 years of age and older" for clarity.
- Section 1: The indications were revised to expand the patient population to include "patients 12 years of age and older."
- Section 2: A clarifying comment was added to state that controlled studies did not extend beyond 16 weeks for the maintenance of healed EE in the pediatric population.

- Section 6: The safety data were revised to include TEAEs occurring in ≥5% of patients since five percent represents a more meaningful cutoff due to the small numbers of patients in these two studies. Data provided are from a pooled analysis of all TEAEs across both study 206 and 207.
- Section 8.4: A statement was added to clarify that the safety and effectiveness of dexlansoprazole has been established in pediatric patients 12 to 17 years of age, including that use in this population is supported by evidence from adequate and well-controlled adult studies, as well as additional safety, efficacy, and PK data from pediatric patients aged 12 to 17 years.
- Section 12.3: A summary of the PK data was added for patients 12 to 17 years of age as compared with adults (refer to clinical pharmacology review by Dr. Shen Li for additional details).
- Section 14.4: The details of the description of the clinical trial data were revised to more accurately reflect the data. A statement was added to specify that the use of Dexilant in this age group is supported by evidence from adequate and well-controlled studies of Dexilant capsules in adults, and is supported by safety and pharmacokinetic studies performed in pediatric patients.

9.3 Advisory Committee Meeting

No advisory committee meeting was held regarding this efficacy supplement.

9.4 Financial Disclosures

Covered Clinical Study (Name and/or Number): TAK-390MR_206

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Applicant of covered study: Takeda		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): TAK-390MR_207

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

9.5 Supplemental Tables/Figures

Table 25: Schedule of Study Procedures (Study 206)

Study Procedures	Screening Period		Treatment Period			Unscheduled Visit (m)	Follow-up Phone Call (5-10 Days Post Treatment)
	Screening Days -21 to -2	Study Visit Day -1	Study Day 1	Week 2 Phone Call	Week 4 Visit/Final Visit/Early Term (a)		
Visit Windows(Days)	+ 5			±3	-4 to + 7		
Visit Number:	1	2		3	4		
Screening Informed Consent and Assent	X						
Study entry Informed Consent and Assent		X					
Inclusion/exclusion criteria assessment	X	X					
Demographics and medical history	X						
Medication history	X						
Concurrent medical conditions	X	X					
PGSQ-A-SF (b)		X			X		
Physical examination	X	X			X	X	
Weight and height	X				X		
Vital signs (c)	X	X			X	X	
Access IVRS/IWRS for Subject number	X						
CYP2C19 Genotype testing					X		
Endoscopy (after subject meets ediary qualification)	X (d)						
Esophageal and gastric biopsies	X (d)						
12-lead ECG (e)	X				X		
Clinical laboratory tests	X						
Fasting clinical laboratory tests (f)		X			X		
Fasting serum gastrin (f)		X			X		
H. pylori CLO test	X (d)						
Hepatitis panel	X						
tTG antibody	X						

(continued on next page)

Study Procedures	Screening Period		Treatment Period				Site Follow-up Phone Call (5-10 Days Post Treatment)
	Screening Days -21 to -2	Study Visit Day -1	Study Day 1	Week 2 Phone Call	Week 4 Visit/Final Visit/Early Term (a)	Unscheduled Visit (m)	
Visit Windows(Days)	+ 5			±3	-4 to + 7		
Visit Number:	1	2			3		
Urinalysis	X	X			X		
Urine pregnancy test for all females	X	X			X		
GERD symptom investigator assessment		X			X		
Electronic daily diary (g)	X	X		X	X	X	
Phone Call				X(k)			X(l)
Access IVRS /IWRS	X	X			X		
Dispense Study medication via IVRS/IWRS (h)		X					
Dispense rescue medication (i)	X	X					
First day of study drug administration			X				
Study drug return and accountability					X		
Return rescue medication (j)		X			X		
Pretreatment event monitoring	X	X					
Adverse event monitoring (l)			X	X	X	X	X
Concomitant medication	X	X		X	X	X	

(source: applicant's submitted "Schedule of Study Procedures, " sNDA22287 submission, TAK-390MR_206 protocol amendment 2, page 70/97.)

(a) Subjects who prematurely discontinue from the Treatment Period should undergo Final Visit procedures no later than 5 days after the last dose of study drug.
(b) The PGSQ-A-SF should be completed prior to any other scheduled study procedure.
(c)Vital signs should be measured prior to all study procedures except the PGSQ-A-SF.
(d) Screening endoscopy must be performed prior to Day -1 but only after subjects have met the diary qualification criteria of heartburn on at least 3 of any 7 days as recorded in the electronic daily diary. The *H. pylori* CLO test will be performed on an additional gastric antral biopsy specimen. Additional esophageal, gastric and duodenal biopsies may be obtained if clinically indicated or part of standard of care, as determined by the investigator.
(e) If the screening ECG is performed on the day of endoscopy, the ECG should be performed prior to endoscopy sedation.
(f) Subjects should be fasting for a minimum of 8 hours prior to all laboratory evaluations. Subjects should be instructed to take their dose of study medication on the morning of their visit with water, applesauce, pureed apples or yogurt (for subjects unable to swallow a capsule) following the expected blood draw. Day -1 fasted clinical laboratory evaluations may be collected either prior to the endoscopy procedure or prior to the Day -1 Visit. If the screening Visit 1 clinical laboratory results are within normal range, they do not need to be repeated if the Day-1 Visit occurs within 7 days of the screening visit. However, a fasting serum gastrin level must be collected on Day-1 Visit for these subjects. After enrollment into the study a 24 hr urine for magnesium excretion will be collected if serum magnesium is ≤1.1 mEq/L (≤0.55 mmol/L).
(g) Subjects should complete the electronic daily diary every morning (for nighttime symptoms) and every evening (for daytime symptoms) on each day of the study. Instruct the subject to continue to complete the electronic daily diary every morning upon waking and evening before bedtime. eDiary review is to be completed at all visits. Return of eDiary upon final visit.
(h) Study drug dispensed on Study Day -1 after the subject has completed all of the Screening Period procedures and subject has met all Inclusion/Exclusion criteria for the study. Study drug will be self administered on Study Day 1 and continued on a daily basis for 4 weeks.
(i) Rescue medication will be dispensed at Screening, and can be dispensed at Study Day -1.
(j) Rescue medication will be returned to assess subject usage.
(k) Study staff will ask the subject about new AEs, review ediary compliance and address any questions about GERD symptoms.
(l) Any spontaneously reported AEs will continue to be reported for 30 days after the last dose of study drug or Early Termination. The study center staff will follow-up with a phone call 5 to 10 days post-treatment and any new AEs will be recorded in the eCRFs and site source document.
(m) If this visit results in premature termination, procedures should be conducted as listed under the Week 4/Final Visit column. Access IVRS / IWRS if additional study drug is needed.

Table 26: Excluded Medication List (applies to Study 206 and Study 207)

Excluded Medications	Period of Exclusion
Prescription or non-prescription H2RA	During screening and throughout the study.
Antacids(a) (except site supplied)	During screening and throughout the study.
PPIs (except study-supplied dexlansoprazole)	One week (7 days) prior to screening, during screening and throughout the study.
NSAIDs, chronic use (>12 doses/month) including COX 2, NSAIDs. Oral or intravenous corticosteroids ≥10 mg of prednisone per day.	Within 30 days prior to pre treatment endoscopy and until last dose of study drug.
Drugs with significant anticholinergic effects such as tricyclic antidepressants or drugs with CNS effects that could mask perception of symptoms (eg, SSRI, benzodiazepines).	During screening and until last dose of study drug. However, subjects who have remained on a stable regimen and dose of these medications for 90 days prior to Day -1 and who agree to maintain the same regimen and dose during the study including the screening and treatment period will qualify. Also, short-term use of anticholinergics for study-related procedures is not exclusionary.
Misoprostol	During screening and until last dose of study drug.
Prokinetics (including metoclopramide, cisapride, tegaserod, bethanechol, erythromycin, domperidone)	During screening and until last dose of study drug.
Anticoagulant or antiplatelet therapy	During screening and until last dose of study drug.

CNS=central nervous system, COX2= cyclo-oxygenase-2, NSAID= nonsteroidal anti-inflammatory drug, SSRI= selective serotonin reuptake inhibitor.
(a) Antacids other than $Mg(OH)_2$ and /or aluminum hydroxide $Al(OH)_3$ or containing simethicone are excluded.

(source: TAKMR_206 study protocol, amendment 2, dated 4/25/13, Table 7.a page 30), TAKMR_207 study protocol, amendment 2, dated 4/25/13, Table 7.a, page 35)

Table 27: GERD Investigator Assessment

Definitions of GERD Symptoms Assessed by Investigator

Symptom	Definition
Heartburn	A burning feeling in the mid-epigastric area and/or chest area.
Acid Regurgitation	Flow of sour or bitter fluid into the mouth.
Dysphagia	Difficulty in swallowing.
Belching	The voiding of gas from the stomach through the mouth, which may have been associated with acid regurgitation.
Epigastric Pain	Central upper abdominal pain.

Definitions of GERD Symptoms Severity by Investigator

Severity	Definition
None	No symptoms.
Mild	Symptom did not last long and was easily tolerated.
Moderate	Symptom caused discomfort and/or interrupted usual activities (including sleep).
Severe	Symptom caused great interference with usual activities and may have been incapacitating (including sleep).
Very Severe	Symptom caused intense and constant discomfort and/or marked interference with usual activities (including sleep).

(source: TAK-MR_206 study protocol (amendment 2), dated 4/25/13, appendix E, page 75.)

Figure 7: Patient Reported Outcome Tool (PGSQ-SF-A)

Pediatric Gastroesophageal Symptom and Quality of Life Questionnaire (Short-Form)

PGSQ-SF Child and Adolescent Version

Completed by Children and Adolescents 9-17 Years of Age

Hello!

We would like to know how you have been feeling over the past 7 days. Please answer the following questions. There are no "right" or "wrong" answers. Everyone has different feelings and will answer these questions differently. If you're not sure how to answer a question, just give the best answer you can.

Instructions:

For each question, you will write an "X" in the box, like this: ☒
So every question will have only one box filled in with an "X".

There is no hurry - you can take as long as you need to answer the questions.

** If you have any questions before you begin or while you're answering the questions, please ask! **

Let's Begin.
Turn the page. ☞

PGSQ-A-SF
September 9, 2011; Ver. 1.0
A-11280

Page 1 of 3

1. Read each statement below and tell us on how many days in the past 7 days you had each of these.

In the past 7 days, on how many days did you…	None (0 days)	1 or 2 days	3 or 4 days	5 or 6 days	Everyday (7 days)
a) have hurting or burning in your stomach above your belly button	☐	☐	☐	☐	☐
b) have hurting or burning in your chest	☐	☐	☐	☐	☐
c) have a sore throat or burning in your throat	☐	☐	☐	☐	☐
d) feel sick to your stomach or nauseated like you might throw up	☐	☐	☐	☐	☐
e) taste throw up in your mouth	☐	☐	☐	☐	☐
f) burp a lot	☐	☐	☐	☐	☐
g) have trouble falling asleep because of any of these problems	☐	☐	☐	☐	☐

Go to the next page. ☞

(continued on next page)

Please Read:

We have a few questions for you about how your stomach/chest problems may have affected your **EVERYDAY LIFE**. There are no "right" or "wrong" answers.

By "stomach/chest" problems, we mean things like stomach pain, chest pain, throat pain, throwing up, and all of the things listed on the previous pages.

2. Please read each statement below and tell us how often you felt that way in the past 7 days.

In the past 7 days…	Never	Almost never	Sometimes	Almost always	Always
a) because of my stomach/chest/throat problems, I didn't feel like doing anything	❒	❒	❒	❒	❒
b) because of my stomach/chest/throat problems, I couldn't eat what I wanted	❒	❒	❒	❒	❒
c) because of my stomach/chest/throat problems, I couldn't drink what I wanted	❒	❒	❒	❒	❒
d) because of my stomach/chest/throat problems, I was in a bad mood	❒	❒	❒	❒	❒

You're finished!
Thank you for filling out this questionnaire!

PGSQ-A-SF
September 9, 2011; Ver. 1.0
A-11280

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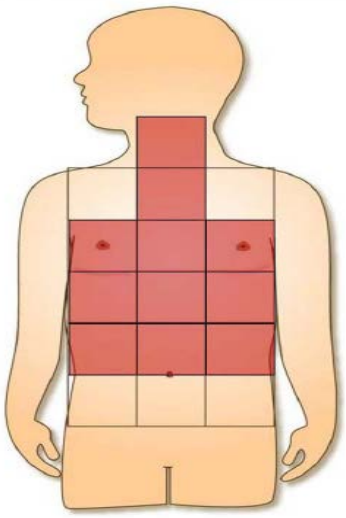
(source: applicant's sNDA22287 submission, TAK-390MR_206 protocol amendment 2, Appendix F, page 78/97.)

Figure 8: eDiary Questions for Adolescents

12-17 Year Pediatric Heartburn Daily Diary Training

In this study you will be asked to complete a diary about your heartburn twice a day. For this study, heartburn means a burning or hurting in your throat, chest, or stomach. A diagram of a human body is included below to show you where you might feel heartburn. The areas shaded in red on the body are places where you might feel heartburn.

You will complete the diary every morning when you wake up and every night before you go to bed.



12-17 year Pediatric Heartburn Daily Diary — Version 1.0 April 1, 2010

Morning Diary

1. Did you have any heartburn (burning or hurting in your throat, chest, or stomach) during the night last night?

   Yes No

2. How much did the burning feeling in your throat, chest, or stomach hurt last night?
   - Did not hurt very much
   - Hurt some
   - Hurt a lot

3. Did you take any antacid during the night?

   Yes No

Evening Diary

1. Did you have any heartburn (burning or hurting in your throat, chest, or stomach) during the day today?

   Yes No

2. How much did the burning feeling in your throat, chest, or stomach hurt during the day today?
   - Did not hurt very much
   - Hurt some
   - Hurt a lot

3. Did you take any antacid during the day?

   Yes No

(source: applicant's sNDA22287 submission, TAKMR-390_206 protocol amendment 2, pages 81-81)

Table 28: LA Classification of Esophagitis

Grade	LA Classification of Esophagitis Grading System Grade Definition
A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
B	One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference
D	One (or more) mucosal break, which involves at least 75 % of the esophageal circumference

(source: applicant's sNDA22287 submission, TAKMR-390_206 protocol amendment 2, Appendix H, page 83)

Table 29: Schedule of Study Procedures (Study 207)

	Screening Period		Treatment Period										
Study Procedures	**Screening Days -21 to -2**	**Study Visit Day -1**	**Study Day 1**	**Week 2 Phone Call**	**Week 4 Visit**	**Week 8 Visit**	**Week 12 Phone Call**	**Week 16 Visit**	**Week 20 Phone Call**	**Week 24 Visit/Final Visit/ Early Term (a)**	**Follow-up phone call (5-10 days)**	**Unscheduled Visit (l)**	**Monthly Follow-up Visits, Week 28, 32, 36 (m)**
Visit Windows(Days)	+5			± 3	± 3	± 4	± 3	± 3	± 3	-4 to + 4			±5
Visit Number:	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**			
Screening informed consent and assent	X												
Study entry informed consent and assent		X											
Access IVRS/IWRS for subject number	X												
Inclusion/exclusion criteria assessment	X	X											
Demographics and medical history	X												
Medication history	X												
Concurrent medical conditions	X	X											
PGSQ-A-SF (b)		X			X	X		X		X			X
Physical examination	X	X			X	X		X		X		X	X
Weight and height	X					X		X		X			X
Vital signs (c)	X	X			X	X		X		X		X	X
CYP2C19 genotype testing					X								
Endoscopy	X (d)					X				X			
Esophageal and gastric biopsy	X (d)												
12-lead ECG (e)	X									X			
Clinical laboratory evaluations	X												
Fasting clinical laboratory evaluations (f)		X			X	X		X		X			X (n)
Fasting serum gastrin (f)		X			X	X		X		X			X (n)
H. pylori test	X (d)												

Continues on next page

	Screening Period		Treatment Period										
Study Procedures	Screening Days -21 to -2	Study Visit Day -1	Study Day 1	Week 2 Phone Call	Week 4 Visit	Week 8 Visit	Week 12 Phone Call	Week 16 Visit	Week 20 Phone Call	Week 24 Visit/Final Visit/ Early Term (a)	Follow-up phone call (5-10 days)	Unscheduled Visit (l)	Monthly Follow-up Visits, Week 28, 32, 36 (m)
Visit Windows(Days)	+5			± 3	± 3	± 4	± 3	± 3	± 3	-4 to + 4			±5
Visit Number:	1	2		3	4	5	6	7	8	9			
Hepatitis panel	X												
tTG antibody	X												
Urinalysis	X	X			X	X		X		X			X (n)
Urine pregnancy test for females	X	X			X	X		X		X			X
GERD symptom investigator assessment		X			X	X		X		X			X
Electronic daily diary (g)	X	X	X	X	X	X	X	X	X	X		X	X
Phone call				X			X		X				
Access IVRS/IWRS	X	X			X	X		X		X			
Dispense study medication (h) via IVRS/IWRS.		X			X	X		X					
First day of study drug administration			X										
Study drug return and accountability (i)					X	X		X		X			
Rescue medication dispense/return (i)	X	X			X	X		X		X			X
Pretreatment event monitoring	X	X											
Adverse event monitoring			X	X	X	X	X	X	X	X	X(j,k)	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X		X	X

CYP=cytochrome P450, ECG=electrocardiogram.
(a) Subjects who prematurely discontinued from the Treatment Period underwent Final Visit procedures no later than 5 days after the last dose of study drug.
(b) The PGSQ-A-SF was completed prior to any other scheduled study procedure.
(c) Vital signs were measured prior to all study procedures except the PGSQ-A-SF.
(d) The Screening endoscopy was performed after subjects met the diary qualification criteria of heartburn on at least 3 of any 7 days as recorded in the eDiary. An endoscopy that was performed within 1 week prior to signing informed consent and assent may have been an acceptable replacement for the Screening endoscopy if it included: the LA Classification of Esophagitis Grading System grade of A-D, biopsies that satisfied the minimum protocol requirements, and endoscopic pictures were obtained. H. pylori assessment must also have been obtained. The screening endoscopy was to be performed prior to Day -1. Gastric and esophageal biopsies were performed during the Screening endoscopy. H. pylori CLO test was performed on the gastric antral biopsy specimen if Screening endoscopy was performed after signing informed consent and assent. If endoscopy was performed prior to signing informed consent and assent, acceptable methods to determine H. pylori status were histology, 13C-urea breath test, CLO test on gastric biopsy or ELISA test for detection of H. pylori antigen in stool. Additional esophageal, gastric and duodenal biopsies may have been obtained if clinically indicated or part of standard of care, as determined by the investigator.
(e) If the Screening ECG was performed on the day of endoscopy, the ECG was performed prior to endoscopy sedation.
(f) Subjects fasted for a minimum of 8 hours prior to all labs. Subjects were instructed to take their dose of study medication on the morning of their visit with water, applesauce, pureed apples, or yogurt (for subjects unable to swallow a capsule) following the expected blood draw. Day -1 fasted clinical laboratory evaluations may have been collected either prior to the endoscopy procedure (if endoscopy was performed after signing informed consent and assent) or at the Day -1 Visit. If the Screening Visit 1 clinical laboratory results were within normal range, they did not need to be repeated if the Day -1 Visit occurred within 7 days of the Screening Visit. However, a fasting serum gastrin level was obtained for these subjects. After enrollment into the study, a 24-hour urine for magnesium excretion was collected if serum magnesium level was ≤1.1 mEq/L (≤ 0.55 mmol/L).
(g) Subjects completed the eDiary every morning (for nighttime symptoms) and every evening (for daytime symptoms) on each day of the study. Subjects were instructed to continue to eDiary completion every morning upon waking and evening before bedtime. The eDiary was reviewed at all visits, and returned at the Final Visit.
(h) Study drug was dispensed on Study Day -1 after the subject completed all of the Screening Period procedures and met all inclusion/exclusion criteria for the study. Dexlansoprazole 60 mg QD was self-administered on Study Day 1 and continued through Week 8. If subjects had endoscopically proven healing of EE, they were randomized to receive either dexlansoprazole 30 mg QD or placebo QD for the remaining 16 weeks.
(i) Study drug and rescue medication were returned at all visits for compliance/usage verification.
(j) Any spontaneously reported adverse events continued to be reported for 30 days after last dose of study drug or Early Termination.
(k) For subjects who completed the study at Week 8 and subjects continued in the study but terminated at or prior to Week 24, study staff followed-up with a phone call 5 to 10 days after last dose of study drug and any new adverse events were recorded in the eCRFs and site source documents.
(l) If an unscheduled visit resulted in premature termination during the Treatment Period, procedures were conducted as listed under the Week 24 column.
(m) Subjects who required an invasive procedure or treatment with a PPI or H2RA for GERD/EE at any time during the Post-Treatment Follow-up Period were discontinued from the study. A Final Visit occurred with procedures from the Post-Treatment Follow-up visits performed.
(n) Fasting clinical laboratory evaluations and fasting gastrin were only performed at Weeks 32, 36 and/or the Final Visit of the Post-Treatment Follow-up Period if the previous assessment showed any abnormalities that required follow-up.

(source: applicant's submission, study TAK-390MR_207 clinical study report, Table 9.c, pages 37-39)

Table 30: Clinical Laboratory Tests (applies to Study 206 and Study 207)

Hematology	Chemistry	Urinalysis
Red Blood Cells White Blood Cells with differential Hemoglobin Hematocrit Platelets MCHC MCV MCH RDW Reticulocyte Count	ALT Albumin Alkaline phosphatase AST Fasting glucose* γ-glutamyltransferase Total cholesterol Total bilirubin Total protein Serum creatinine Blood urea nitrogen Calcium Phosphorus Potassium Magnesium** Chloride Bicarbonate or carbon dioxide Sodium Uric acid Iron TIBC Ferritin 25-OH-D Vitamin B12	Specific gravity pH Protein Ketones Glucose Bilirubin Blood Leukocyte Esterase Microscopic Analysis (only if positive dipstick results): RBC/high-power field WBC/high-power field Epithelial cells, casts etc
Other: CYP2C19 isoenzyme (blood or buccal swabs)		
Serum	**Urine**	
Hepatitis panel, including HBsAg, Anti-HCV, Anti-HAV-IgM and Hepatitis E IgG and IgM Fasting gastrin tTG antibody	Urine Pregnancy test (females) Magnesium**	

(source: Applicant's submission, Clinical Study Reports, TAK-390MR_206, Table 9.e, page 40, or TAK390MR_207, Table 9.e, page 44.)

Table 31: Takeda Medically Significant AEs

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizures	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

(source: applicant's submission, protocol incorporating ammendment 2, TAK-390MR_206, page 51.)

Table 32: Analysis Cutoffs for Critically Abnormal Hematology Parameters

Parameter	Applicant Provided Critical Range
Hemoglobin	<0.8x LLN or >1.2x ULN
Hematocrit	<0.8x LLN or >1.2x ULN
RBC count	<0.8x LLN or >1.2x ULN
WBC count	<0.8x LLN or >1.2x ULN
Platelet count	<75,000 cells/uL or > 600,000 cells/uL

(source: applicant's submission, Table 15.3.4.1.2, "Criteria for Markedly Abnormal Values of Laboratory Parameters")

Table 33: Analysis Cutoffs for Critically Abnormal Chemistry Parameters

Albumin	<2.5g/dL	None
Total Protein	< 0.8x LLN	None
Sodium	<130 mEq/L	None
Sodium	>150 mEq/L	5 patients
Potassium	<3.0mEq/L or > 5.3mEq/L*	None
Creatinine	>1.0 mg/dL*	8 patients
AST	>3x ULN	None
ALT	>3x ULN	None
GGT	>3x ULN	None
Total Bilirubin	>2x ULN	1 patient

*(Source: applicant's submission, Table 15.3.4.1.2, "Criteria for Markedly Abnormal Values of Laboratory Paratmeters.") *Analysis parameters for Creatinine and Potassium were altered to more conservative cutoffs as described in the review in section 7.4.2.*

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/s/

TARA A ALTEPETER
06/23/2016

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