CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-287

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 15, 2009
From	Ruyi He, MD Acting Deputy Director/Medical Team Leader Division of Gastroenterology Products/ODE III
Subject	Cross-Discipline Team Leader Review
NDA	22-287
Applicant	TAP Pharmaceutical Products Inc.
Date of Submission	December 31, 2007
PDUFA Goal Date	January 31, 2009
Proprietary Name / Established (USAN) names	Kapidex (dexlansoprazole) Delayed Release Capsules Ref. IND 69,927
Dosage forms / Strength	Kapidex (dexlansoprazole) Delayed Release Capsules (30, 60 (b) (4) mg)
Proposed Indication(s)	1. Healing (b) (4) of all grades of erosive esophagitis (EE) 2. Maintaining healing of EE (b) (4) 3. Treating (b) (4) heartburn (b) (4) associated with gastroesophageal reflux disease (GERD)
Recommended:	I concur with Dr. Tamara Johnson's recommendations that NDA 22-287, Kapidex (dexlansoprazole) Delayed Release Capsules, be approved in adult population for the following 3 indications: 1. Healing of all grades of EE 2. Maintaining healing of EE 3. Treating heartburn associated with GERD. For the indication of healing of all grades of EE, I recommend that 60 mg once daily be approved and (b) (4) once daily be not approved. For the indications of maintaining healing of EE and treating heartburn associated with GERD, I recommend that 30 mg once daily be approved and (b) (4) once daily be not approved. The higher dexlansoprazole doses did not provide additional clinical benefit over that of lower dexlansoprazole dose for all 3 indications.

1. Introduction

Gastroesophageal reflux disease (GERD) is a common recurring medical problem in the United States, with a prevalence of GERD-related symptoms at least once a month in approximately 40% of patients. GERD comprises a spectrum of acid-related disorders, including nonerosive GERD and erosive esophagitis (EE).

Proton Pump Inhibitors (PPIs) suppress gastric acid secretion by specific inhibition of the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell, and are the most effective medications for relieving GERD symptoms, healing the injured mucosa, maintaining a healed mucosa, and preventing the development of complications.

Dexlansoprazole is the R-enantiomer of lansoprazole that was approved in the US in 1995 for a variety of acid-related gastrointestinal disorders, including healing of EE, maintenance of healed EE, and symptomatic GERD. Lansoprazole has a chiral center and 2 enantiomers: R- and S-lansoprazole.

In this NDA application, the sponsor seeks marketing authorization for Kapidex (dexlansoprazole) Delayed Release Capsules for the following indications:

- Healing (b) (4) of all grades of EE
- Maintaining healing of EE (b) (4)
- Treating (b) (4) heartburn (b) (4) associated with GERD

The NDA includes 2 Phase 3 studies to support each of the indications and a long-term uncontrolled study.

2. Background

GERD is a common recurring medical problem and a number of risk factors, such as advancing age, obesity, smoking, and alcohol and caffeine consumption have all been associated with the development of GERD. The physical presence of gastric acid in the esophagus is believed to be necessary for GERD to develop, and the severity of symptoms is related to the duration of acid exposure. 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. EE is defined as the presence of superficial esophageal erosions in patients with or without typical GERD symptoms.

EE is diagnosed during endoscopy in up to 50% of patients with GERD symptoms. The severity of these symptoms is associated with the extent and duration of gastric acid exposure in the esophagus. 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, the premalignant condition of Barrett's esophagus and esophageal adenocarcinoma.

Therapy for GERD is largely focused on the prevention of reflux of gastric acid into the esophagus, either by pharmacological or surgical means, with surgery usually reserved for intractable cases. Pharmacological management of GERD includes treatment with antacids, histamine-receptor antagonists, prokinetic agents, and PPIs. PPIs are the most effective medications for relieving GERD symptoms, healing the injured mucosa, maintaining a healed mucosa, and preventing the development of complications.

3. CMC

Based on CMC review team's assessment, this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, a site recommendation from Office of Compliance has not been made as of the date of this review. CMC reviewer, Dr. Tarun Mehta, recommended that the NDA be not approved until the site recommendation from Office of Compliance become available.

Drug Substance
Drug substance Dexlansoprazole is a R-enantiomer of the approved racemic (1:1 ratio) drug lansoprazole. Dexlansoprazole (API) is a new active ingredient in enantiomeric form.

Dexlansoprazole is pale yellowish white crystalline powder. It is freely soluble in polar organic solvent but practically insoluble in non-polar organic solvent. It is slightly soluble in water (0.16mg/mL), but become soluble (58mg/mL) at the pH value of 10.9. Starting and intermediate materials for manufacturing dexlansoprazole and lansoprazole are the same (b) (b) (4) . The degradation products of the dexlansoprazole are similar to that of the lansoprazole. According to Dr. Tarun Mehta, no new impurities were discovered during the synthesis as well as in the stability studies. The sponsor has submitted adequate information on manufacturing process and API characterization in this NDA. Adequate in-process controls are in place in manufacturing process to assure the consistent quality of the drug substance.

Based on the stability data of clinical stability batches and, according to ICH Guidance Q1E, a retest date of (b) (4) is granted.

Drug Product
The drug product dexlansoprazole Modified Released Capsules are available in 30, 60 (b) mg strength. Modified capsules are filled with two types of enteric coated granules (4) exhibiting dual delayed release mechanism. One type of granules will release the drug in the proximal region of the small intestine where the pH reaches approximately 5.5. The second type of granules will release the drug more distally in the intestine where the pH reaches approximately 6.75. The ratio of these granules is maintained at (b) (pH 5.5: pH 6.75). The formulation components of both the granules are the same except for the enteric coating layer.

The drug product specification is deemed satisfactory, according to CMC reviewer, Dr. Tarun Mehta. The drug products were stored up to 18 months for 30mg and 24 months for 60 and

(b) strengths at 250C/60% RH condition. The results met the specification and no significant trend was observed. Therefore, 24 months of expiration dating period for the drug product is granted.

In conclusion, based on CMC review team's assessment, the sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. For detail CMC assessment, please see Dr. Tarun **Mehta's review dated December 23, 2008.**

4. Nonclinical Pharmacology/Toxicology

Pharmacology studies indicated that Dexlansoprazole was more potent than the racemic lansoprazole on the inhibition of basal gastric acid secretion in rats.

In the 4-week and the 13-week oral toxicity studies in rats, Wistar rats were treated by oral gavage with Dexlansoprazole at 0, 15, 50, and 150 mg/kg/day. There were no treatment related changes in mortality, clinical signs of toxicity, ophthalmology, and urinalysis. Histopathological examination revealed eosinophillic change in chief cells of the stomach and liver hypertrophy in all treatment groups.

In the 13-week oral toxicity study in dogs, Beagle dogs were treated by oral capsule with Dexlansoprazole at 0, 5, 15, and 50 mg/kg/day for 13 weeks. There were no treatment related changes in mortality, body weight, ophthalmology, ECG, hematology, clinical chemistry, and urinalysis. Clinical signs of toxicity such as vomiting and soft/watery feces were noted in the treatment groups. Histopathological examination revealed vacuolation and necrosis of parietal cells of stomach in all treatment groups including lansoprazole. In the liver, bile thrombus was also noted in one male each at high dose of both Dexlansoprazole and lansoprazole and one female each at mid dose Dexlansoprazole and lansoprazole. The liver and stomach were the target organs of toxicity. The results indicated that both dexlansoprazole and lansoprazole have similar toxicity profiles.

Dexlansoprazole was positive in the Ames tests and in the in vitro chromosomal aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the in vivo micronucleus test in mice and was not teratogenic in the segment II reproductive toxicity study in rabbits.

Dexlansoprazole had no effects on the ECG and platelet count at doses up to 50 mg/kg/day in the 13-week oral toxicity study in dogs. The blood pressure was not monitored in this study. Lansoprazole had no effects on the blood pressure and heart rate at i.d. dose of 300 mg/kg in anesthetized cats and at i.d. dose of 150 mg/kg in dogs. To further investigate the potential cardiac ischemic effects of dexlansoprazole, Dr. Zhang recommend that the sponsor be asked to conduct studies with dexlansoprazole on platelet aggregation using human peripheral platelets as a phase 4 commitment. However, according to the regulatory briefing discussion, majority of people who attended the Briefing did not consider dexlansoprazole caused the

potential cardiac ischemic effects. Therefore, studies with dexlansoprazole on platelet aggregation using human peripheral platelets are not necessary.

In conclusion, according to Dr. Zhang, approval of dexlansoprazole is recommended for the proposed indications. For detail information, **please see Dr. Ke Zhang's review dated** December 1, 2008.

5. Clinical Pharmacology/Biopharmaceutics

According to the clinical pharmacology team's assessment, the application is acceptable. Regarding the proposed doses for individual indications, the clinical pharmacology team agrees with clinical team and recommends that the (b) daily not be approved for healing EE (b) (4) daily dose not be approved for maintenance of healed EE.

Pharmacokinetic characteristics:
Dexlansoprazole binds to human plasma proteins extensively (~96%) over the concentration range of 1-20 μg/ml. Following single oral dose in healthy subjects, plasma $AUC_{(0-48)}$ and Cmax of dexlansoprazole increased approximately dose proportionally between 30mg and 60mg, and less than dose proportionally between 60 mg and 120 mg. The half-life was 3-3.7 hours. Cross-study comparisons showed that patients with symptomatic GERD had higher mean dexlansoprazole AUC than healthy subjects (46% to approximately 76% higher).

CYP2C19 polymorphism:
Following single oral dose of 30 mg and 60 mg, the heterozygous extensive metabolizers (EMs) (*1/mutant allele) had approximately 2-fold and 1.3-fold higher Cmax and 2.2 fold and 1.4--fold higher AUC values than the homozygous EMs(*1/*1), respectively. At 90 mg and 120 mg, both Cmax and AUC were similar between these two groups. Poor metabolizers (PMs, mutant allele/mutant allele) had AUC values 2.96, 5.44, 4.67, 3.41, and 3.5 fold higher than EMs (homozygous and heterozygous EMs combined) when dosed with 15 mg, 30 mg, 60 mg, 90 mg, and 120 mg dexlansoprazole MR QD, respectively.

Food effect:
When a single 90-mg dose was administered 30 minutes to 1 hour before or 30 minutes after the start of a high-fat meal, dexlansoprazole Cmax increased by 36 to 52% and AUC increased by 30-33% relative to administration while fasting. There were also effects of food on both t_{max} and early-phase absorption. When drug was administered 30 minutes *after* a meal, early-phase absorption was significantly impaired and t_{max} was delayed by 2-4 hours relative to administration before or meal or while fasting. When drug was administered *before* a meal, the rate of early-phase absorption is not affected relative to administration while fasting.

A separate, single-dose (60 mg) study in Japanese men who were CYP2C19 extensive metabolizers found that Cmax increased by 45% and AUC increased by 14% when dexlansoprazole was administered after a meal relative to fasting.

When the drug was administered 30 minutes to 1 hour before a high fat meal, there were no clinically significant differences in intragastric pH over the dosing interval between the fed and fasting regimens. When the drug was administered 30 minutes *after* a meal, there was a delay in the increase of gastric pH. Therefore, dexlansoprazole may be taken with or without food but there is a possible delay in onset of the effect if the drug is administered with or after a meal. In addition, there was no difference in dexlansoprazole exposure when administered as an intact capsule or as granules sprinkled over applesauce.

Metabolism/Excretion:
Human liver microsomes preferentially converted dexlansoprazole and lansoprazole to 5-hydroxylansoprazole over lansoprazole sulfone with formation of 5-hydroxylansoprazole correlating well with CYP2C19 activity, whereas formation of lansoprazole sulfone correlating well with CYP3A4 activity. In a mass balance study with [C14]dexlansoprazole, mean (SD) radioactivities recovered in urine and feces after 7 days were 37.2% (4.0%) and 44.4% (7.0%) of the administered dose, respectively. Dexlansoprazole was the major component in the plasma, accounting for over 70% of the plasma radioactivity. Dexlansoprazole was metabolized by oxidation, reduction, and conjugation to at least 19 metabolites with ten metabolites detected in plasma.

Drug drug interactions:
Dexlansoprazole inhibit in-vitro hepatic CYP 2C19 activity. In-vitro studies showed that lansoprazole is a CYP 1A1 and 1A2 inducer.

A single dose of 250 mg phenytoin, a CYP2C9 substrate, was administered following 6 doses of dexlansoprazole 90 mg. No significant interaction was observed based on the AUC and Cmax of phenytoin. A single 25 mg dose of warfarin, another CYP2C9 substrate, was administered following 6 doses of dexlansoprazole 90 mg. No significant interaction was observed based on the AUC, Cmax, of R- and S-warfarin and INR.

Special populations:
The differences in the pharmacokinetics of dexlansoprazole between healthy subjects and patients with moderate hepatic impairment reached statistical significance for Cmax, AUCt, and AUC∞. Dose reduction in patients with hepatic impairment is recommended.

Dexlansoprazole exhibited higher AUC in the elderly (30.7% higher) or female subjects (40.6% higher) than in the young or male subjects, respectively, though the differences did not reach statistical significance.

QT effect:
The QT/IRT review team concludes that "No significant QT prolongation effect of dexlansoprazole (90 mg and 300 mg) was detected in this TQT study."

Exposure/response relationship:
Following repeated dose for 5 days, intra-gastric pH values were similar between 60 mg and 120 mg. No advantage in increasing intragastric pH was observed at doses higher than 60 mg. The mean percent time when intragastric pH exceeded 4 was similar between 60 and 120 mg.

Though the exposure increases with dose between 30 mg and 120 mg, there is no clear pharmacodynamic response (intragastric pH & percent time of intragastric pH exceeded 4) and exposure relationship between 60 mg and 120 mg. The data further support the recommendations that the (b) (4) daily not be approved for healing EE and the (b) (4) daily dose not be approved for maintenance of healed EE.

For detail information, please see Dr. Jane Bai and Dr. Kristina Estes's review dated by December 3, 2008.

6. Clinical Microbiology

NA

7. Clinical/Statistical- Efficacy

The NDA included a total of 6 Phase 3, randomized, controlled studies conducted to evaluate the efficacy and safety of dexlansoprazole for the 3 proposed indications. The maintenance of healed EE studies enrolled subjects who were healed in the healing of EE studies. Both healing of EE studies and 1 maintenance of healed EE study (T-EE05-135) were conducted at sites in the US and up to 19 other countries. The remaining studies were conducted in the US only.

Lansoprazole 30 mg QD was chosen as the comparator in the healing of EE studies because it is the approved dose for this indication. Placebo was included in the maintenance of healed EE and symptomatic GERD studies as it is often used as a standard comparator to evaluate efficacy and safety in these indications. In addition, the use of placebo allows evaluation of the clinical benefits of maintenance therapy and the risk of relapse when active treatment is discontinued.

Demographic and Other Characteristics of the Study Population

Across all treatment groups in all Phase 3 studies, the majority of subjects were White (84% to 87%) and >45 years of age (57% to 62%). In the healing of EE studies (N=4092) and maintenance of healed EE studies (N=896), there were approximately equal numbers of males and females enrolled. In the symptomatic GERD studies (N=1855), the majority of subjects were female (71%). Within each study, there were no statistically significant differences between treatment groups for any of the baseline demographic characteristics.

In the 2 healing of EE studies, approximately 71% of enrolled subjects had EE Grades A or B, and 29% had Grades C or D (6% were Grade D).

Both Helicobacter pylori (H pylori)-positive and H pylori-negative subjects were enrolled in the symptomatic GERD studies. H pylori-positive subjects were excluded from enrolling in the healing of EE studies. This exclusion was due to the fact that H pylori infection could potentially have a confounding effect on efficacy in EE healing. This factor is not known, or

considered, to impact the relief of symptoms in nonerosive GERD subjects. Barrett's esophagus was an exclusion criterion in all dexlansoprazole Phase 3 studies.

Efficacy Results

Healing of EE

Two identical, multicenter, randomized, double-blind, active-controlled, 3-arm studies were conducted to assess the efficacy and safety of dexlansoprazole 60 mg and 90 mg compared to lansoprazole 30 mg. The primary efficacy endpoint, healing of EE by Week 8, was assessed using a closed testing procedure by first assessing non-inferiority of the dexlansoprazole doses to lansoprazole. If a dexlansoprazole dose was shown to be non-inferior to lansoprazole, then it was tested for superiority. The secondary efficacy endpoints were: healing of EE by Week 4 and the healing of LA Grades C and D by Week 8.

Efficacy results are summarized in Table 1 below.

Table 1: Summary of Healing Rates of EE by Week 8 ITT Subjects

Data Set Analysis	Dexlansoprazole MR 60 mg QD % (95% CI)	Dexlansoprazole MR 90 mg QD % (95% CI)	Lansoprazole 30 mg QD % (95% CI)	p-value Dex MR 60 mg vs Lanso	p-value Dex MR 90 mg vs Lanso	p-value Dex MR 60 mg vs Dex MR 90 mg
Study T-EE04-084						
By Crude (Primary)[a]	(N=639) 85.3 (82.3, 87.9)	(b) (4)	(N=656) 79.0 (75.6, 82.0)	0.004*	(b) (4)	(b) (4)
By Life Table (Supportive)[b]	(N=673) 92.3 (90.0, 94.7)	(b) (4) (b) (4)	(N=684) 86.1 (83.0, 89.2)	0.060	(b) 9	(b) (4)
Study T-EE04-085						
By Crude (Primary)[a]	(N=657) 86.9 (84.1, 89.4)	(b) (4)	(N=648) 84.6 (81.6, 87.3)	0.234	(b) (4)	(b) (4)
By Life Table (Supportive)[b]	(N=685) 93.1 (90.9, 95.3)	(b) (4)	(N=672) 91.5 (89.0, 93.9)	0.167	(b) (4)	(b) (4)
Integrated Analysis						
By Crude (Primary)[a]	(N=1296) 86.1 (84.1, 87.9)	(b) (4)	(N=1304) .7 (79.5, 83.8)	0.003*	(b) (4)	(b) (4)
By Life Table (Supportive)[b]	(N=1358) 92.7 (91.1, 94.4)	(b) (4) (b) (4)	(N=1356) 88.9 (87.0, 90.9)	0.021*	(b) (4)	(b) (4)

Note: Endoscopic assessments conducted >7 days after the last dose of study drug are excluded.
CI=confidence interval; Dex MR=dexlansoprazole MR; Lanso=lansoprazole 30 mg QD.

a Primary analysis: p-values are from CMH test with Baseline LA Grade as strata.
b Supportive analysis: p-values are from log-rank test with day as a discrete time unit.
* Dexlansoprazole MR treatment group is statistically significantly superior to lansoprazole 30 mg QD using Hochberg's method at the nominal level of 0.05.

Dexlansoprazole 60 mg and 90 mg demonstrated non-inferiority to lansoprazole 30 mg and both were highly effective in healing by Week 8 (Table 1).

Dexlansoprazole 60 mg and 90 mg daily were statistically superior to lansoprazole 30 mg daily in the study 084. However, in the study 085 Dexlansoprazole 60 mg was not statistically superior to lansoprazole 30 mg daily (p=0.234). Although the 90 mg dose of Dexlansoprazole

was statistically superior to lansoprazole 30 mg daily in the study 085, the multiplicity adjustment procedure used by the sponsor is not wildly accepted according to Dr. Cooner, FDA statistician. This statistical superiority cannot be confirmed by using a more **conservative multiplicity adjustment approach according to FDA statistician's evaluation (Dr. Freda Cooner's review).**

The therapeutic gains of dexlansoprazole 60 mg and 90 mg over lansoprazole 30 mg for overall healing rates at Week 8 were (b) (4) I concur with Dr. Keith St. Amend that the treatment differences between Dex 90 mg and lansoprazole 30 mg in each study are not clinically meaningful (b) (4)

The enrollment of nearly 30% of subjects with moderate to severe EE (baseline LA Grade C or D) was intended to gather more data in this important subset. For the secondary endpoint **"Week 8 healing for baseline LA Grades C or D," efficacy results are summarized in Table 2.**

Table 2: Week 8 Healing Rates by Baseline LA Grade C or D

Data Set Analysis	Dexlansoprazole MR 60 mg QD % (95% CI)	Dexlansoprazole MR 90 mg QD % (95% CI)	Lansoprazole 30 mg QD % (95% CI)	p-value Dex MR 60 mg vs Lanso	p-value Dex MR 90 mg vs Lanso	p-value Dex MR 60 mg vs Dex MR 90 mg
Study T-EE04-084						
Week 8 C or D by Crude (Primary)[a]	(N=182) 79.7 (73.1, 85.3)	(b) (4) (b) (4)	(N=200) 65.0 (58.0, 71.6)	0.002#	(b)	(b)
Week 8 C or D by Life Table (Supportive)[b]	(N=191) 88.9 (83.7, 94.2)	(b) (4) (b) (4)	(N=208) 74.5 (67.3, 81.6)	0.011#	(b) (4)	(b)
Study T-EE04-085						
Week 8 C or D by Crude (Primary)[a]	(N=194) 77.8 (71.3, 83.5)	(b) (4) (b) (4)	(N=190) 78.9 (72.5, 84.5)	0.768	(b) (4)	(b) (4)
Week 8 C or D by Life Table (Supportive)[b]	(N=199) 87.6 (82.2, 92.9)	(b) (4) (b) (4)	(N=194) 87.7 (82.4, 93.0)	0.727	(b) (4)	(b) (4)
Integrated Analysis						
Week 8 C or D by Crude (Primary)[a]	(N=376) 78.7 (74.2, 82.8)	(b) (4) (b) (4)	(N=390) 71.8 (67.0, 76.2)	0.030	(b) (4)	(b) (4)
Week 8 C or D by Life Table (Supportive)[b]	(N=390) 88.2 (84.5, 92.0)	(b) (4) (b) (4)	(N=402) 81.5 (77.0, 86.0)	0.037	(b) (4)	(b)

The Study 084 showed a statistically significant therapeutic gain for the 60 mg dose when compared to lansoprazole 30 mg (79.7% vs. 65%), but this dose failed to show a similarly significant gain in the second study (Study 085) or in the integrated analysis. In fact, the treatment response for the lansoprazole group was slightly higher than that of the Dex 60 mg group for the second study (79% vs. 78%, Table 2).

The 90 mg Dex did not show statistical superiority in either study when compared to the active comparator. Although the sponsor compared the 90 mg treatment group to the 60 mg group and found a statistically significant difference, no adjustments for multiplicity were made. For **detail efficacy evaluation, please see Dr. St. Amand's review.**

Maintenance of Healed EE

Two double-blind, multicenter, randomized, placebo-controlled, maintenance of healed EE studies were conducted to compare the efficacy and safety of dexlansoprazole with that of placebo. The primary measure of efficacy was maintenance of healing at Month 6. The rates of maintenance of healed EE were estimated using 2 methods: crude rates and time-to-event methods. The crude rate analysis was the primary analysis for maintenance rates. This crude rate analysis was conservative, because subjects who prematurely discontinued with their last endoscopy showing no recurrence were considered to have recurred. Maintenance rates based on the time-to-event method are the rates commonly used.

Table 3: Rates for Maintenance of Healed EE at Month 6, ITT Primary Subjects

% (95% CI)	Placebo	30 mg Dex	60 mg Dex	90 mg Dex
Study 135 Crude Rates	N=119 14.3 (8.5, 21.9)	N=125 66.4 (57.4, 74.6)	(b) (4)	
Study 135 Life-Table Rates	N=145 27.2 (18.3, 36.0)	N=137 74.9 (67.2, 82.6)		
Study 086 Crude Rates	N=112 14.3 (8.4, 22.2)	NA		
Study 086 Life-Table Rates	N=140 25.7 (17.0, 34.4)	NA		

The results of these studies showed that dexlansoprazole was highly effective in the maintenance of healed EE. Within 1 month of discontinuing the active treatment that healed their EE, nearly two-thirds of the placebo patients had relapsed, and by 6 months, the relapse rate was greater than 85% in the placebo group (35% in the dexlansoprazole groups), highlighting the importance of continuing effective maintenance therapy.

In these studies, all 3 doses of dexlansoprazole (30 mg, 60 mg, and 90 mg) were superior to placebo in maintaining healed EE. In each study, the doses of dexlansoprazole demonstrated statistically significantly higher rates of maintenance of healed EE (approximately 65% for all dexlansoprazole doses compared to 14% for placebo) by the primary crude rate analysis. The maintenance rates for the supportive time-to-event methods ranged from (b) (4) for all dexlansoprazole doses compared to 27% for placebo (Table 3).

The 6-month relapse rates observed for the dexlansoprazole doses (34%) were consistent with those seen in the public literatures (the Cochrane review), which reported an overall relapse rate of 36% among randomized trials using maintenance doses of PPIs.

The study evaluated the dexlansoprazole 60 mg and 90 mg doses and demonstrated that dexlansoprazole 60 mg and 90 mg did not provide additional clinical benefit over that of dexlansoprazole 30 mg. No significant differences between 60 mg and 30 mg or between 90 mg and 60 mg were seen.

As a secondary endpoint prospectively defined by the sponsor, percentage of 24-hour heartburn-free days during treatment (neither daytime nor nighttime heartburn) was analyzed.

The percentage of 24-hour heartburn-free days during treatment was statistically significantly higher in subjects in the dexlansoprazole treatment groups (median range: 90.9% to 96.1%) compared to the placebo treatment group (medians range: 19.2% to 28.6%). However, there are several potential issues that did not address in Dr. St. Amand's review and may change the degree of treatment effect.

The potential issues include imbalance at baseline for number of days with heartburn, imbalance at baseline for mean severity and imbalance at baseline for rescue medication use between the patients in 30 mg Dexlansoprazole group and placebo group. However, the imbalances are small and should not change the conclusion of the studies. (b) (4) Based on the data evaluated by Dr. St. Amand, it is acceptable to state that the percentage of 24-hour heartburn-free days during treatment was higher in subjects in the dexlansoprazole treatment groups compared to the placebo treatment group.

Symptomatic GERD

Two double-blind, randomized, placebo-controlled GERD studies were conducted to compare the efficacy and safety of dexlansoprazole with that of placebo. Relief of heartburn during both daytime and nighttime combined over 4 weeks was the primary efficacy endpoint.

In both symptomatic GERD studies, all doses of dexlansoprazole (30 mg, 60 mg, and 90 mg) demonstrated significantly superior relief of heartburn combined compared to placebo over a 4-week treatment period, with no additional clinical benefit observed for doses greater than 30 mg.

The results presented in Table 4 show evidence of efficacy for all doses of dex when compared to placebo. The treatment differences are 22 to 25%. There was no significant difference seen between any two dex doses, and there is no evidence of a dose-response trend. This is consistent with the studies performed in support of the other indications for this NDA as well.

The treatment difference seen with the 30 mg dose of dex translates to approximately 7.1 fewer days with neither daytime nor nighttime heartburn in one month of treatment. I agree with Dr. St. Amand that dex 30 mg provides clinically meaningful benefit to patients when compared to placebo, and that no additional benefit is derived from the higher doses of dex studied for this indication.

Efficacy results are summarized in Table 4.

Table 4: Summary of Percentage of Days Without Heartburn

	Placebo	30 mg Dex	60 mg Dex	90 mg Dex
Study 137			(b) (4)	
N	310	312		
Median	18.5	54.9		
Mean (SD)	25 (25.6)	50.3 (33.9)		
Study 082				
N	290	NA		
Median	17			
Mean (SD)	24.9 (25.7)			
Integrated				
N	600	312		
Median	17.8	54.9		
Mean (SD)	25 (25.6)	50.3 (33.9)		

In each controlled study, the percentage of days that subjects had no nighttime heartburn during treatment, according to daily electronic diary, was statistically significantly greater in both dexlansoprazole treatment groups (30-mg QD and 60-mg QD in Study T-GD05-137, and 60-mg QD and 90-mg QD in Study T-GD04-082) than in the placebo treatment group. No statistically significant difference was observed between the dexlansoprazole treatment groups for this endpoint in either study. The dexlansoprazole 60-mg QD dose was the only dexlansoprazole dose that was used in both of the Phase 3 symptomatic GERD studies, and the data for this dose were consistent between the 2 studies. In addition, the integrated analysis supported the results from the individual studies.

Of the 5 approved prescription PPIs currently on the market, (b) (4) carries an indication for the treatment of "(b) (4) (b) (4) (b) (4) The approval for "(b) (4) (b) (4) was based on secondary endpoints of two small studies, and it is unable to confirm what methodology was used to adjust for the multiplicity of examining these secondary endpoints for use in labeling, I concur with Dr. St. Amand that the approval of (b) (4) does not provide an adequate historical basis for approving the language sought (b) (4) by the sponsor for dexlansoprazole.

A scientific basis for granting a claim for the specific treatment of (b) (4) heartburn is equally elusive. The epidemiology of (b) (4) GERD is not well-studied and experts have been unable even to agree on an accepted definition for the condition as Dr. St. Amand stated in his review.

The symptoms of nocturnal reflux may not be due solely to the patients' supine position as is often supposed; rather, they may be due largely to the numerous physiologic mechanisms which are altered during sleep, including decreased rate of swallowing, diminished salivary production, and reduced upper esophageal sphincter basal pressure. This overall alteration in esophageal defense mechanisms leads to prolonged acid exposure at night, which is associated

with increased risk of severe GERD manifestations, including erosive esophagitis, peptic **stricture, Barrett's esophagus and adenocarcinoma of the esophagus.**

I concur with Dr. St. Amand that **the indication should be "treat**ment of heartburn associated **with non-erosive GERD." Any further parsing of the underlying disease of GERD into "(b) (4) heartburn" for a la**beling claim seems unnecessary based on the biopharmaceutical profile of the product and minimally clinically useful based on the current scientific understanding of the disease process.

8. Safety Evaluation

This NDA contains safety data for 5072 subjects who received ≥1 dose of dexlansoprazole (30 mg QD to 300 mg QD) as of 14 January 2008, the database cut-off. A total of 4548 subjects were exposed to study drug in the total dexlansoprazole group (one or more of these doses: 30 mg, 60 mg, or 90 mg) during the Phase 3 studies.

Across all of the Phase 3 studies, 863 subjects in the total dexlansoprazole group received ≥1 dose of dexlansoprazole 30 mg, 60 mg or 90 mg for ≥24 weeks and 203 subjects for ≥ 48 weeks. Dexlansoprazole have not been approved in any country yet.

Mean age of all dexlansoprazole subjects was 47.8 years and mean body mass index (BMI) was 29.8 kg/m^2. No differences were observed between treatment groups for any baseline demographic characteristic, with the exception of gender. The gender difference in the placebo and dexlansoprazole 30-mg QD treatment groups is due to the fact that a greater percentage of females (71%) compared to males participated in the Phase 3 symptomatic GERD studies. This gender difference is consistent with the non-erosive GERD population. Across the Phase 3 study groups by indication and the long-term safety study, no differences were observed with respect to any other baseline demographic characteristic.

Deaths
Seven subjects (5 dexlansoprazole 60 mg QD [0.09/100 Patient-months of exposure (PM)], 1 dexlansoprazole 90 mg QD [0.02/100 PM], 1 lansoprazole 30 mg QD [0.06/100 PM]) died in the Phase 3 studies. There is no death in the placebo group. Of these 7 subjects, 1 subject was in the symptomatic GERD studies, 3 subjects were in the healing of EE studies, and 3 subjects were in the long-term safety study. No dose-dependent trend was noted. In addition, no trends were identified regarding the types or onset of treatment-emergent adverse events leading to death or the cause of death, and all were considered by the investigator to be not related to study drug.

A listing of these subjects from the Phase 3 studies is provided in Table 5.

Table 5: listing of Adverse Events Resulting in Death in the Phase 3 Studies

Subject No./ Gender/Age[a]/ Study No.	MedDRA High Level Term/*MedDRA Preferred Term*	Day of Onset[b]	Relationship to Study Drug	Cause of Death	Day of Death
Dexlansoprazole MR 60 mg QD					
11382007/M/45/ T-GD04-082	Poisoning and Toxicity/*Therapeutic Agent Toxicity*	17 (3)	Not Related	Acute methadone toxicity	17 (3)
32457009/M/48/ T-EE04-084	Hepatic Failure and Associated Disorders/ *Chronic Hepatic Failure* Coma States/*Coma Hepatic* General Nutritional Disorders NEC/*Malnutrition*	78 (75) 78 (75) 78 (75)	Not Related Not Related Not Related	End stage liver disease, hepatic coma, and malnutrition	88 (85)
11333014/F/50/ T-EE04-085	Gastric Neoplasms Malignant/*Gastric Cancer*	-54[c]	Not Related	Stomach cancer	83 (72)
32128005/F/78/ T-GI04-088	Leukaemias, Acute Myeloid/*Acute Promyelocytic Leukaemia*	33 (1)	Not Related	Severe respiratory failure secondary to acute promyelocytic leukaemia	52 (20)
9223002/F/45/ T-GI04-088	Respiratory Failures (Excl Neonatal/*Acute Respiratory Failure*	377 (1)	Not Related	Acute respiratory failure[d]	377 (1)
Dexlansoprazole MR 90 mg QD					
9172013/F/64/[e] T-GI04-088	Staphylococcal Infections/ *Staphylococcal Sepsis*	113 (1)	Not Related	Sepsis due to fracture of right elbow, repaired	114 (2)
Lansoprazole 30 mg QD					
32460061/F/58/ T-EE04-084	Non-Site Specific Procedural Complications/*Procedural Complication*	42 (13)	Not Related	Liposuction surgery	42 (13)

Note: Adverse events were coded using MedDRA Version 10.0.
a Age at time of enrollment.
b Relative to first day of dosing. Days postdosing shown in parentheses.
c Estimated by investigator.
d This subject had a history of asthma (data from the Pharmacovigilance database).
e This subject received treatment with dexlansoprazole MR during Study T-GD04-082.

Nonfatal Serious Adverse Events (NFSAE) in All Phase 3 Studies Combined
Sixty-eight subjects, of the 6,807 participating in the Phase 3 clinical trials, reported ≥1 treatment-emergent nonfatal serious adverse events (NFSAE).

Examining the proportion of NFSAE by treatment group showed the highest risk among the Dexlansoprazole treatment groups. The Dexlansoprazole had approximately 3 to 6 times higher NFSAE risk than its comparators: 0.9% for 30mg, 1.1% for 60mg, and 1.2% for 90mg dexlansoprazole, versus 0.2% for placebo and 0.5% for lansoprazole.

Because the durations of treatment were different among the treatment groups, we did further analyses using patient-months (PM) of exposure to adjust the total duration of exposure. Overall NFSAE incidence rates were 0.43/100PM among 30mg dexlansoprazole, 0.49/100PM among 60mg dexlansoprazole, 0.49/100PM among 90mg dexlansoprazole, versus 0.19/100PM among placebo and 0.39/100PM among 30mg lansoprazole treatment groups. The total Dexlansoprazole treatment population demonstrated 1.2-2.5 x higher non-fatal SAE incidence rates than lansoprazole 30mg or placebo.

Table 6: Treatment-Emergent Nonfatal Serious Adverse Events in Each Groups by Percentage and per 100 PM of Exposure in All Phase 3 Studies Combined

	Placebo N=896 PM=1.2	Dex 30mg N=455 PM=2.1	Dex 60mg N=2311 PM=2.3	Dex 90mg N=2142 PM=2.8	Dex Total N=4548 PM=2.7	Lan 30mg N=1363 PM=1.3
N (%)	2 (0.22)	4 (0.88)	26 (1.13)	29 (1.35)	59 (1.30)	7 (0.51)
N (*100 PM)	2 (0.19)	4 (0.43)	26 (0.49)	29 (0.49)	59 (0.48)	7 (0.39)

* Average 100 Patient-months of exposure

Summarized from Sponsor's Table 18 in the 4-Months Safety Update, pp. 61-69.

There were 2 patients with SAEs, 1 spontaneous abortion and 1 coronary artery occlusion in the placebo group. Severn patients with SAEs in the lansoprazole group were cholecystitis, CVA, bipolar disorder, small intestinal obstruction, facial palsy, hemiparesis, and pneumonia.

Most of 59 patients with SAEs in the dexlansoprazole group are in the following 2 groups: cardiovascular SAEs and fractures (injuries). They are summarized in the table below.

Table 7: Treatment-Emergent Nonfatal Serious Adverse Events interested per 100 PM of Exposure in All Phase 3 Studies Combined

	Placebo N=896 *PM=1.2	Dex Total N=4548 PM=2.7	Lan 30mg N=1363 PM=1.3
Cardiovascular SAE (PM)	1 (0.09)	18 (0.15)	1 (0.05)
Fractures and Injuries (PM)	0	11 (0.09)	0
Syncope/vertigo and fall (PM)	0	8 (0.07)	0

* Average 100 Patient-months of exposure. A patient may have more than 1 event in different system

Summarized from Sponsor's Table 18 in the 4-Months Safety Update, pp. 61-69.

The higher rate of Cardiovascular-Related Nonfatal SAEs was found in the dexlansoprazole group than either placebo (0.15 per 100 PM vs. 0.09 per 100 PM) or lansoprazole group (0.15 per 100 PM vs. 0.05 per 100 PM) as shown in the table 7. The highest rate (0.42 per 100 PM) was found in the 30 mg dexlansoprazole group (table 8). However, there is no difference for the cardiovascular SAE between the 90 mg dexlansoprazole group and placebo group and it may indicate that the higher cardiovascular SAE observed in the 30 mg dexlansoprazole group may not be due to treatment (dexlansoprazole).

Table 8. Cardiovascular-Related Nonfatal Serious Adverse Events in All Phase 3 Studies

CARDIOVASCULAR-RELATED SAEs	Treatment Group: n (rate per 100 PM)					
	Placebo	Dexlansoprazole				Lansop.
	(N=896) (Avg. PM=1.2)	30 mg QD (N=455) (Avg. PM=2.1)	60 mg QD (N=2311) (Avg. PM=2.3)	90 mg QD (N=2142) (Avg. PM=2.8)	Total (N=4548) (Avg. PM=2.7)	30 mg QD (N=1363) (Avg. PM=1.3)
Ischemic CAD	0	2 (0.21)	1 (0.02)	1 (0.02)	4 (0.03)	0
Cerebrovascular Accident	0	1 (0.11)	0	0	1 (<0.01)	1 (0.05)
Heart Failure	0	1 (0.11)	0	0	1 (<0.01)	0
CAD NEC	1 (0.09)	0	1 (0.02)	1 (0.02)	2 (0.02)	0
Chest Pain	0	0	4 (0.08)	2 (0.03)	6 (0.05)	0
Pulmonary Embolism	0	0	0	1 (0.01)	1 (<0.01)	0
Cerebral Venous Thrombosis	0	0	1 (0.02)	0	1 (<0.01)	0
DVT	0	0	1 (0.02)	0	1 (<0.01)	0
TIA	0	0	1 (0.02)	0	1 (<0.01)	0
Total cardiovascular SAE	**1 (0.09)**	**4 (0.42)**	**9 (0.17)**	**5 (0.08)**	**18 (0.15)**	**1 (0.05)**

In the OSE consultation review, Dr. Diane Wysowski concluded that there is not **dose/response (adverse events) relationship and "It does not seem likely that dexlansoprazole is a cause of cardiovascular disorders in the clinical trial data." For detail OSE assessment, please see Dr. Diane Wysowski's review.**

The Injury-Related Nonfatal Serious Adverse Events in All Phase 3 Studies were summarized in Table 9.

The Injury-Related Nonfatal Serious Adverse Events in All Phase 3 Studies were reported only in the Dexlansoprazole treatment groups. There was no case in the either placebo or lansoprazole group. The incidence rates display a dose-related trend where incidence (0, 0.11, and 0.25 subjects per 100PM) increases with increasing doses (30mg, 60mg, and 90mg Dexlansoprazole, respectively). The incidence of fall was notable for 90mg Dexlansoprazole, being 3x higher than that of the 60mg dosage, in a similarly sized population. The sponsor assured that no instances of fall were associated with symptoms of dizziness or lightheadedness. It is unclear whether injury-related SAE observed in the studies were related to dexlansoprazole treatment. Post-market study for such events may be useful.

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Table 9: Injury-Related Nonfatal Serious Adverse Events in All Phase 3 Studies

INJURY-RELATED SAEs	Treatment Group: n (rate per 100 PM)					
	Placebo	Dexlansoprazole MR				Lansoprazole
	(N=896) (Avg. PM=1.2)	30 mg QD (N=455) (Avg. PM=2.1)	60 mg QD (N=2311) (Avg. PM=2.3)	90 mg QD (N=2142) (Avg. PM=2.8)	Total (N=4548) (Avg. PM=2.7)	30 mg QD (N=1363) (Avg. PM=1.3)
Fall	0	0	1 (0.02)	4 (0.06)	5 (0.04)	0
Foreign Body Trauma	0	0	1	0	1	0
Injury	0	0	1	0	1	0
Syncope	0	0	1	1	2	0
Vertigo Positional	0	0	0	1	1	0
Ankle Fracture	0	0	0	1	1	0
Musculoskeletal Discomfort	0	0	0	1	1	0
Rib Fracture	0	0	0	1	1	0
Upper Limb Fracture	0	0	0	1	1	0
Limb Injury	0	0	1	0	1	0
Back Injury	0	0	1	0	1	0
Intervertebral Disc Protrusion	0	0	0	2	2	0
Joint Instability	0	0	0	1	1	0
All NFSAE Injury-related	***0***	***0***	***6 (0.11)***	***13 (0.22)***	***19 (0.16)***	***0***

Adapted from Sponsor's Table 18. Treatment-Emergent Nonfatal Serious Adverse Events per 100 PM of Exposure in All Phase 3 Studies in the 4-Months Safety Update, pp. 61-69.

Potential Cardiovascular Adverse Events in All Phase 3 Studies Combined

Dr. Johnson performed a review of cardiovascular events across all dexlansoprazole Phase 3 studies with combination of severe adverse events and non-severe adverse events. The number of subjects in the total dexlansoprazole group with ≥1 treatment-emergent potential cardiovascular adverse event interested per 100 PM of exposure was 0.56/100 PM which is 2 times higher than that (0.28/100 PM) in the placebo or Lansoprazole group (Table 10).

Majority of potential cardiovascular AE (36/69, 52%) in the dexlansoprazole group were chest **pain and chest discomfort. Etiology is unknown. According to the sponsor's analysis, chest** pain and chest discomfort were **secondary to patients' underlined** diseases (EE or GERD). It is difficult to conclude the clinical significance from this observation.

Because of this potential safety concern, DGP consulted the OSE. In the OSE consultation review, Dr. Diane Wysowski concluded that there is not dose/response (adverse events) **relationship and "It does not seem likely that** dexlansoprazole is a cause of cardiovascular **disorders in the clinical trial data." For detail OSE assessment, please see Dr. Diane Wysowski's review.**

Table 10: Treatment-Emergent potential cardiovascular Adverse Events interested per 100 PM of Exposure in All Phase 3 Studies Combined

	Placebo N=896 *PM=1.2	Dex Total N=4548 PM=2.7	Lan 30mg N=1363 PM=1.3
Cardiovascular AE: N (PM)	3 (0.28)	69 (0.56)	5 (0.28)
Specific AEs	2 chest pain 1 CAD	21 chest pain 9 CAD 3 heart failure 15 chest discomfort 3 CVA 1 TIA 8 arrhythmia 5 DVT/PE 4 cardiac/vascular disorder NEC	3 chest pain 1 CVA 1 DVT

* Average 100 Patient-months of exposure

Discontinuation

The table below summarized the primary reason for discontinuation in the healing of EE studies.

Table 11: Summary of the Primary Reason for Discontinuation in the Healing of EE studies

	Dexlansoprazole MR		Lansoprazole	
Primary Reason for Discontinuation	**60 mg QD (N=1374) n (%)**	**90 mg QD (N=1355) n (%)**	**30 mg QD (N=1363) n (%)**	**All Subjects (N=4092) n (%)**
Total Subjects Prematurely Discontinued	104 (8)*	89 (7)	76 (6)	269 (7)
Adverse Event	31 (2)*	17 (1)	16 (1)	64 (2)
Protocol Violation	3 (<1)	1 (<1)	3 (<1)	7 (<1)
Lost to Follow-Up	17 (1)	18 (1)	16 (1)	51 (1)
Withdrew Consent	25 (2)	29 (2)	25 (2)	79 (2)
Did Not Meet Inclusion/Exclusion Criteria	17 (1)	9 (<1)	10 (<1)	36 (<1)
Other	11 (<1)	15 (1)	6 (<1)	32 (<1)
Lack of efficacy	2	2	0	4
Noncompliance	2	3	3	8
Possible Barrett's esophagus	5	7	2	14
Subject request/subject unavailable	1	2	0	3
Abnormal laboratory findings	0	0	1	1
Investigator decision	1	1	0	2

* Indicates statistical significance versus lansoprazole 30 mg QD ($p \leq 0.05$) using Fisher's exact test.

From this table you can see that more patients in the Dexlansoprazole 60 mg group discontinued therapy secondary to adverse events than that in the Lansoprazole group (2% vs. 1%). However, it was not seen in the 90 mg group. Otherwise, there is no significant difference between the treatment group and control group for the primary reasons of discontinuation.

Laboratory
The review of laboratory data saw no statistically significant difference between Dex and comparator treatment groups for hepatic enzymes, gastric polyps, and hematology. There were no Hy's law cases. There were statistically significant differences between Dex and its comparators for chemistry, urinalysis, vital signs, and weight; but these changes were not clinically meaningful. Dexlansoprazole was not found to prolong the QT/QTc interval. Dexlansoprazole increased serum gastrin levels as is expected with all PPIs.

Dexlansoprazole is not currently approved or marketed in any country, thus, there are no postmarketing reports available.

For detail safety evaluation of NDA 22-287, **please see Dr. Tamara Johnson's review.**

9. Regulatory Briefing

A regulatory briefing was held on 10/10/08 in reference to the safety concerns arising in this application. The purpose was to decide whether these concerns warrant additional studies from the sponsor either prior to approval or post approval. Recommendations regarding the following 3 questions are discussed below.

1 Do you have concerns on the excess adverse events (AE) observed in the dexlansoprazole treatment groups compared to the lansoprazole or placebo group in Phase 3 studies?
   a. Serious adverse events
   b. Cardiovascular events
   c. Fractures/injury-related events

2. What is your recommendation for regulatory action?
   a. Complete Response with additional study to evaluate the potential AE
   b. Approval without additional study
   c. Approval with PMR for additional study to evaluate the potential AE

3. What types of study do you recommend, if additional study is needed?

The regulatory briefing panel, composed of CDER senior management officials, acknowledged the imbalance of adverse events between dexlansoprazole and its comparators in regards to cardiovascular and fracture/injury-related events. The majority of the panel members considered that the safety profile of Dexlansoprazole is acceptable. The panel

recommended approval of the lowest effective dose of dexlansoprazole without additional study.

10. Pediatrics

The Pediatrics consultation review indicated that since **none of the PPI's is approved in** patients less than 1 year of age, conducting pediatric studies with the drug would represent a therapeutic benefit over the other PPIs. For older age groups, a new PPI may not represent a therapeutic benefit per se, unless the agent possesses a better safety profile or affords easier dosing. Since the study of lansoprazole in patients less than one year did not demonstrate effectiveness, a different endpoint and/or study design is likely to be required.

The sponsor provides a pediatric assessment plan in the NDA submission. This plan has been presented to the CDER pediatric committee. The committee concurred the plan to WAIVE pediatric study in patients 0-1 months and DEFER studies in patients 1-17 years. The sponsor agreed to conduct following studies in the following age groups.

12-Year to 17-Year Old Subjects
The pathophysiology, symptoms and signs, and complications of GERD in adolescents 12 to 17 years of age are similar to those in adults. Additionally, the pharmacokinetics of histamine H^2-receptor antagonists and PPIs, the agents commonly used for treatment of GERD, are similar in these groups. The pharmacokinetic and pharmacodynamic effects of the racemate lansoprazole in adolescents 12 to 17 years of age are also similar to those in adults. Based on these factors, the effects of dexlansoprazole in adolescents 12 to 17 years of age are expected to be similar to those in adults. Therefore, it is acceptable to extrapolate pediatric effectiveness for all 3 indications (healing of EE, maintenance of healed EE, and symptomatic GERD) in this pediatric population from the adequate and well-controlled studies in adults.

The sponsor will conduct a Phase 1, randomized, open-label, multicenter study to evaluate the pharmacokinetics and safety of dexlansoprazole (all approved adult doses) in adolescents with symptomatic gastroesophageal reflux disease (GERD). The study will be conducted to confirm that the pharmacokinetic profile following multiple doses (7 days) of dexlansoprazole in adolescents 12-17 years of age is similar to the pharmacokinetic profile observed in adults.

The sponsor will also conduct a Phase 2 study to bridge the safety and efficacy of dexlansoprazole to the adult studies in symptomatic GERD and EE.

The sponsor plans to submit the study reports by March 31, 2013.

1-Year to 11-Year Old Subjects
The pathophysiology, symptoms and signs, and complications of GERD in 1-year to 11-year old subjects are similar to those in adults. The pharmacokinetic and pharmacodynamic effects of the racemate lansoprazole in 1-year to 11-year old subjects are also similar to those in adults. Based on these factors, the effects of dexlansoprazole in 1-year to 11-year old subjects are expected to be similar to those in adults.

It is acceptable to extrapolate pediatric effectiveness in this pediatric population from the adequate and well-controlled studies in adults. The sponsor is planning to conduct the following studies in 1-11 year old subjects, to supplement the adult studies:

- A Phase 1, randomized, open-label, multicenter study to evaluate the pharmacokinetics and safety of dexlansoprazole (15 mg, 30 mg, or 60 mg) in pediatric subjects ages 1 to 11 years old with symptomatic gastroesophageal reflux disease (GERD).

- A Phase 2 study to evaluate the safety and efficacy of dexlansoprazole in 1-year to 11-year old subjects with GERD (including subjects with symptomatic nonerosive GERD and erosive esophagitis) after 8 weeks of treatment.

The deferral date is October 31, 2013.

1-Month to 11-Month Old Subjects
In the 1 to 11 month age group (infants), the pathophysiology of GERD may be similar to that in adults. The pharmacokinetic/pharmacodynamic data for lansoprazole from infants demonstrates that the exposure response profile for lansoprazole observed in infants is generally similar to adults, however lower doses are required for infants ≤10 weeks of age. Although lansoprazole did not demonstrate efficacy in this age group, it is not known whether dexlansoprazole will be efficacious in this age group.

After developing an age appropriate formulation, the sponsor plans to conduct the following studies in 1-11 month old subjects, to supplement the adult studies:

- A Phase 1, Randomized, Open-Label, Multicenter Study to Evaluate the Pharmacokinetics and Safety of dexlansoprazole MR in Pediatric Subjects Ages 1 to 11 Months with GERD.

- A Phase 3 study to evaluate the safety and efficacy of dexlansoprazole versus a control (placebo or active) in subjects 1 to 11-months old with GERD.

The study will be conducted to evaluate the safety and efficacy of dexlansoprazole in infants with GERD. The proposed deferral date is July 31, 2016.

0- to 1-Month Old Subjects
The sponsor was granted a waiver for the racemate, lansoprazole in the 0- to 1-Month old age group, because necessary studies in this age group are impossible or highly impractical. I recommend the request of waiver for dexlansoprazole in the 0 to 1 month patients be granted.

The North American Society for Pediatric Gastroenterology and Nutrition's guidelines for evaluation and treatment of gastroesophageal reflux in infants and children recommend conservative management (e.g., positioning, change to hypoallergenic formulas, food thickening, avoidance of tobacco smoke), for 1 to 2 weeks after the problem is identified. If conservative management is not effective, diagnostic evaluations (endoscopy, pH monitoring)

are recommended, followed by pharmacologic treatment if needed. As this process lasts at least 1 month, it is impractical to enroll children younger than 1 month into GERD trials.

11. Other Relevant Regulatory Issues

DSI was consulted and the inspection was performed as a PDUFA data audit for NDA 22-287. An audit of all subjects' records was conducted. Inspection revealed several protocol violations in that the endoscopy and physical examination for one subject was done by a physician not listed as a sub-investigator on the 1572, the electronic diaries were not reviewed or marked as reviewed by the clinical investigator, and the endoscopic pictures for two subjects were not included with the reports in their source documents as the protocol required. Also there were discrepancies between the eCRFs and source documents in the number of rescue medication returned for 3 subjects.

DSI concluded that these violations would not affect the validity of the data. The data from the three sites inspected are valid and can be used in support of the NDA.

12. Labeling

A tradename review was previously conducted under IND 69,927 (b) (4) was not recommended in the previous tradename review and this was communicated to the sponsor in a letter dated, 12/17/07. (b) (4) was not recommended either. The sponsor's third review name, KAPIDEX, was found acceptable by the tradename review team.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with Dr. Tamara Johnson's recommendations that NDA 22-287, Kapidex (dexlansoprazole) Delayed Release Capsules, be approved in adult population for the following 3 indications:

1. Healing of all grades of EE
2. Maintaining healing of EE
3. Treating heartburn associated with GERD.

For the indication of healing of all grades of EE, I recommend that 60 mg once daily be approved and (b) (4) once daily be not approved.

For the indications of maintaining healing of EE and treating heartburn associated with GERD, I recommend that 30 mg once daily be approved and (b) (4) once daily be not

approved. The higher dexlansoprazole doses did not provide additional clinical benefit over that of lower dexlansoprazole dose for all 3 indications.

- Risk Benefit Assessment

I concur with Dr. Tamara Johnson's Risk Benefit Assessment listed in her review. Dexlansoprazole belongs to the drug class of proton pump inhibitors (PPI) which now have 5 products on the market. Dexlansoprazole has demonstrated greater benefit for the symptomatic GERD and erosive esophagitis patient populations when compared to placebo. Although dexlansoprazole may not provide additional benefit over the 5 currently marketed PPIs, the benefit of dexlansoprazole outweighs the risk of adverse events. Safety concern about a potentially increased risk of ischemic cardiovascular adverse events among dexlansoprazole 30 mg subjects was diminished due to previous cardiac medical history in the subjects and absence of similarly increased risk among dexlansoprazole 60mg and 90mg treatment groups. The sponsor should be asked to conduct study to further evaluate a potential concern of fracture/injury-related adverse events, which occurred at greater incidence with dexlansoprazole than its comparators.

- Recommendation for Postmarketing Risk Management Activities

  None

- Recommendation for other Postmarketing Study Commitments

I concur with Dr. Tamara Johnson's recommendation that the sponsor conduct post-marketing study to further investigate the potential safety risks of fracture/injury-related adverse events.

- Recommended Comments to Applicant

None

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