CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-287

SUMMARY REVIEW

Division Director Summary Review

Date	January 30, 2009
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA#	22-287
Applicant Name	TAP Pharmaceutical products, Inc.
Date of Submission	December 31,2007
PDUFA Goal Date	January 31, 2009
Proprietary Name / Established (USAN) Name	Kapidex Delayed Release Capsules/dexlansoprazole
Dosage Forms / Strength	Delayed release capsules (30mg, 60mg,(b) (b)
Proposed Indication(s)	1. Healing(b) (4) (of all grades of erosive esophagitis 2. Maintaining healing of erosive esophagitis (b) (4) 3. Treating(b) (4) (heartburn (b) (b) (4) associated with gastroesophageal reflux disease (GERD)
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Keith St. Amand, MD Tamara Johnson, MD
Statistical Review	Freda Cooner, PhD/Stella Grosser, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Ke Zhang, PhD
CDTL Review	Ruyi He, MD
CMC Review	Tarun Mehta, PhD/Patrick Marroum, PhD/Moo-Jhong Rhee, PhD
Clinical Pharmacology Review	Jane Bai, PhD/Kristine Estes, PhD/Sue-Chi Lee, PhD
DDMAC	Shefali Doshi/Kathleen Klemm
DSI	Khairy Malek, MD/Constance Lewin, MD, MPH
CDTL Review	Ruyi He, MD
OSE/DMEPA	L.S. Toombs, PharmD/K.C. Arnwine, PharmD/ Todd Bridges, RPH/D. Hamilton-Stokes, RN, BSN
OSE/Division of Epidemiology	Diane Wysowski, PhD/Solomon Iyasu, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Division Director Review

1. Introduction

Dexlansoprazole is the R-enantiomer of lansoprazole, a proton pump inhibitor with a chiral center and 2 enantiomers: R-lansoprazole and S-lansoprazole. Lansoprazole was approved in 1995. It carries the following indications:

a. Short-term treatment of active duodenal ulcer
b. H.pylori eradication to reduce the risk of duodenal ulcer recurrence
c. Maintenance of healed duodenal ulcers
d. Short-term treatment of active benign gastric ulcer
e. Healing of NSAID-associated gastric ulcer
f. Risk reduction of NSAID-associated gastric ulcer
g. Gastroesophageal reflux disease (GERD)
   i. Short- term treatment of symptomatic GERD. "....treatment of heartburn and other symptoms associated with GERD"
   ii. Short-term treatment of Erosive Esophagitis. "...for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis."
h. Maintenance of Healing of Erosive Esophagitis (EE)
i. Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The Applicant proposes to market multiple dose levels of dexlansoprazole, the R-enantiomer of the approved racemic drug, for the following indications:

a. Treatment of (b) (4) heartburn (b) (4) associated with GERD.
b. Healing and (b) (4) relief of all grades of Erosive Esophagitis (EE)
c. Maintenance of healing of EE (b) (4)

Six phase 3 studies were submitted in this application to support these proposed indications. I will focus my summary review on the major review issues identified by the individual discipline review teams. The Applicant's proposed indications do expand the scope of labeling currently approved for lansoprazole for its GERD and EE indications. The Applicant has proposed including the language (b) (4) to the heartburn descriptor of symptoms associated with GERD. In addition the applicant has proposed adding (b) (4) (b) (4) to the maintenance of EE healing indication. Although the Applicant proposed marketing (b) dose levels (30 mg, 60 mg, (b) (4)), the FDA reviewers did not find that the highest proposed dose (b) (4) , resulted in additional clinical benefit for healing erosive esophagitis. In addition the reviewers did not find that the highest dose proposed for the maintenance of healing of erosive esophagitis (b) (4) resulted in incremental improvement of clinical benefit. The reviewers did not recommend approving the (b) (4) dose for any indication and recommended the 60 mg dose only for use in healing erosive esophagitis.

2. Background

Gastroesophageal reflux disease (GERD) is a common disorder. Symptoms are caused by backflow of gastric contents and acid into the esophagus. [1] Symptoms include heartburn, regurgitation of sour material into the mouth, and chest pain. Esophageal pH monitoring has documented that <20% of reflux episodes in patients with documented GERD are associated with symptoms.[2] Erosive esophagitis is mucosal injury manifested by ulcerations, exudate and mucosal friability.

Proton pump inhibitors, which suppress gastric acid secretion through inhibition of the H+,K+-ATPase system of the gastric parietal cell secretory surface, are effective for relieving GERD symptoms and healing erosive esophagitis. Lansoprazole, a PPI approved for treatment of GERD and erosive esophagitis, is a molecule that contains a chiral center. Lansoprazole is a racemic mixture of R- and S- enantiomers, present in a 1:1 ratio. The applicant has developed the R-enantiomer, dexlansoprazole, for marketing as a new drug product. This is analogous to the marketing of proton pump inhibitor esomeprazole, which is the S-enantiomer of the racemic mixture drug omeprazole.

There are multiple proton pump inhibitors currently marketed, including products approved for nonprescription use. The safety record for this class of drug has been good, although there are reports in the literature suggesting that prolonged use might be associated with increased risk of hip fractures.

3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months for the drug product. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The clinical safety reviewer raised questions regarding possible cardiotoxicity during the course of her review. The pharmacology reviewer examined the nonclinical database for evidence of cardiac toxicity. There was no evidence of cardiac toxicity in the 4-week and 13-week oral toxicity studies in rats or the 13-week oral toxicity dog study. Dexlansoprazole had no observed impact on ECGs or platelet counts in the dog study. Dr. Zhang suggested that a phase 4 commitment to study the effects of dexlansoprazole on platelet aggregation be considered in light of the review concerns raised by the clinical safety reviewer. The clinical safety reviewer's concerns, the OSE consultants' recommendations and the pharmacologist's

[1] Harrison's Internal Medicine 17th Edition Online (2008). Chapter 286 Diseases of the Esophagus. Raj K. Gopal.

[2] ACP Medicine (Online) Editors David C Dale and Daniel Federman. Gastroenterology. Esophageal Disorders. Michael F Vaezi, 2007.

review findings were taken to a CDER Regulatory Briefing. The CDER managers and staff at the CDER Regulatory Briefing discussed the nonclinical and clinical data and determined that the cardiac adverse events in the clinical safety data base were not treatment related. (See more detailed discussion in Section 8 Safety.)

I concur with the conclusions reached by the pharmacology reviewer that there are no outstanding issues that preclude approval. Dr. Zhang has recommended a postmarketing platelet aggregation study be conducted as a post marketing commitment. In light of the content of the discussion at the Regulatory Briefing, I do not believe such a study is necessary. I concur with the findings of the CDER officials at the Regulatory Briefing and do not believe the higher proportion of nonfatal myocardial infarctions observed in the lowest dexlansoprazole dose studied reflects a true safety signal.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The clinical pharmacology reviewers recommended that the (b) (4) dose should not be approved for healing erosive esophagitis (the (b) indication for which the Applicant proposed labeling the (b) (4) dose level) and that the (b) (4) dose should not be approved for maintenance of healed erosive esophagitis (EE). I concur with this recommendation because evidence did not support that these higher dose levels were associated with improved clinical benefit.

Dexlansoprazole is metabolized by CYP2C19. The clinical pharmacology reviewers noted that poor metabolizers had 3-5 fold higher AUC values than extensive metabolizers across the dose levels recommended for approval. Heterozygous extensive metabolizers administered a single dose of dexlansoprazole 30 mg and 60 mg had a higher C_{max} and AUC than homozygous extensive metabolizers.

In vitro assays demonstrate that dexlansoprazole inhibits CYP2C19 and induces CYP1A1 and CYP1A2.

Evaluation of pharmacokinetic data from special populations included a hepatic impairment study in which subjects with normal hepatic function and subjects with moderately impaired hepatic function were administered dexlansoprazole 60 mg. The C_{max} in the subjects with hepatic impairment was approximately 1.5 times higher than the C_{max} in subjects with normal hepatic function. The AUC doubled. The clinical pharmacology reviewers recommended that the proposed product label be modified to inform health care providers that a lower dose of dexlansoprazole should be considered for patients with moderate hepatic impairment. The final label states that no adjustment is necessary for patients with mild hepatic impairment and that the 30 mg dose should be considered for patients with moderate hepatic impairment.

The QT/IRT review team evaluated the data from a thorough QT study of dexlansoprazole and concluded that there is no significant QT prolongation effect associated with dexlansoprazole doses of 90 mg and 300 mg.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant proposed 3 indications in this NDA, and submitted six phase 3 studies for review – two for each proposed indication. (b) (4) dose levels were proposed for marketing approval, and the Applicant evaluated multiple dose levels within the clinical trials. My summary of the efficacy review will be organized by (b) (4) beginning with healing of erosive esophagitis, followed by maintenance of healing of erosive esophagitis (b) (4) and ending with the symptoms of GERD (b) (4).

The studies conducted to evaluate healing of erosive esophagitis were not placebo controlled trials, since there is approved therapy for this condition and it was not considered ethical to withhold treatment in the context of a clinical trial for patients who suffer from erosive esophagitis. The control arm for the erosive esophagitis studies was the racemic mixture product, lansoprazole, which is approved for treatment of erosive esophagitis. The studies for healing of erosive esophagitis were designed as noninferiority trials. The studies conducted for the remaining proposed indications included a placebo arm and were designed to show superiority to placebo.

Proposed Indication: Healing of Erosive Esophagitis (EE)

Two randomized, active-controlled, double blind, multicenter studies of identical design were conducted. Both included 3 arms: 1) Dexlansoprazole 90 mg, 2) Dexlansoprazole 60 mg, and 3) Lansoprazole 30 mg (approved dose for treatment of erosive esophagitis). Study duration was 8 weeks. The primary endpoint, healing of EE, was assessed with endoscopy at 8 weeks.

The dexlansoprazole results in the two submitted studies were presented both as "crude rates" and Life table analyses. The crude rates were considered the primary analysis by the clinical and statistical reviewers, and were calculated considering those subjects with missing data at week 8 treatment failures. In the Life Table analyses, which were considered supportive analyses, patients with missing data were dropped from the denominator at the point that they last provided data. The crude rate analysis is the most conservative analysis.

The planned analysis was to test noninferiority of both dexlansoprazole doses to lansoprazole with an overall significance level of 0.05 using Hochberg's method. The Biostatistical reviewer noted in her review that although the Applicant's analysis plan did prespecify that noninferiority to lansoprazole would be declared for both doses if the lower bounds of both 95% confidence intervals of the differences (relative to lansoprazole) were not lower than -10%, they did not support their selection of that margin. The analysis plan included a test for superiority if the dexlansoprazole dose level was found to be noninferior to lansoprazole.

The treatment effect of the active control, lansoprazole 30 mg, is described in its label. The 3 clinical studies of erosive esophagitis include a single placebo controlled trial. The healing

rates reported in the label at 8 weeks in the placebo controlled trial were 95% for lansoprazole and 53% for placebo.

The crude rates for healing in the two studies submitted to this NDA were higher in the dexlansoprazole arms than the lansoprazole arms. This yielded lower bounds for the differences that were quite low. The Biostatistical reviewer evaluated these data, both for the ITT population and the per protocol populations, utilizing a 95% confidence interval and a 97.5% confidence interval, and found that the maximum lower bound in these analyses was only -2.15%. The small observed difference between study arms, which fell well within the Applicant's selected margin, gave the reviewer confidence in concluding that the efficacy of dexlansoprazole had been established for this indication. She concluded that noninferiority to lansoprazole had been demonstrated for both the 60 mg and 90 mg dexlansoprazole dose levels.

Step wise testing for superiority indicated the 60 mg dexlansoprazole dose level was superior to lansoprazole in one study, but not in the other. The 90 mg dexlansoprazole dose level was reported as superior to lansoprazole in both studies. However, after adjustment of alpha, Biostatistical Reviewer Dr. Cooner, Ph.D. did not find 90 mg statistically significantly superior to lansoprazole. When directly compared to each other, no significant difference between the two dexlansoprazole dose levels (60 and 90 mg) was observed in either study, or in the pooled Integrated Analysis of Efficacy. The data are summarized in the table below, which is reproduced from Dr. Ruyi He's Cross Discipline Team Leader (CDTL) review.

Table 1: Summary of Healing Rates of Erosive Esophagitis by Week 8 in ITT Population (reproduced from Dr. Ruyi He's CDTL review).

	Dexlansoprazole MR			p-value		
Data Set Analysis	60 mg QD % (95% CI)	90 mg QD % (95% CI)	Lansoprazole 30 mg QD % (95% CI)	Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	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) (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) (4)	(b) (4)
Study T-EE04-085						
By Crude (Primary)[a]	(N=657) 86.9 (84.1, 89.4)	(b) (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) (b) (4)	(N=1304) 81.7 (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)	(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.

As a prespecified secondary analysis, efficacy was evaluated in the subset of patients who had moderate to severe EE (LA Grade C or D) at baseline. Nearly 30% of the enrolled patients fell into this disease severity category. These analyses demonstrated that the 60 mg dose level was effective in the severe subgroup, and the reviewers did not find that the 90 mg dose level provided additional benefit relative to the 60 mg dose level.

(b) (4) the reviewers recommended that (b) (4) the dexlansoprazole 60 mg dose level should be approved for this indication. I concur with this decision.

Maintenance of Healed Erosive Esophagitis (EE)

The Applicant conducted two double-blind, placebo controlled, multicenter studies to evaluate the ability of dexlansoprazole to maintain healing of erosive esophagitis. Both studies (Study 135 and Study 086) were 3-arm trials and explored two dose levels of dexlansoprazole for 6 months. One placebo controlled study included the dexlansoprazole dose levels evaluated in the "healing of erosive esophagitis trials" – a dexlansoprazole 90 mg arm and a dexlansoprazole 60 mg arm. The other placebo controlled study evaluated a lower dexlansoprazole dose and included dexlansoprazole 60 mg and 30 mg arms.

The primary efficacy endpoint of the studies was maintenance of healing at Month 6, documented by endoscopy. The rates of maintenance were evaluated as crude rates and by Life Table analysis. The crude rate analysis, the more conservative analysis, was the primary analysis. Patients who did not undergo a 6 month endoscopy were considered treatment failures in the crude rate analysis.

The efficacy results from these two studies are summarized in the table below, which is reproduced from Dr. Ruyi He's CDTL review. The studies demonstrated that dexlansoprazole at all dose levels studied – 30 mg, 60 mg, and 90 mg - is superior to placebo in maintaining healing of erosive esophagitis. No convincing additional clinical benefit was observed with either of the two highest dexlansoprazole doses relative to the 30 mg dose. There was no significant difference found in the comparison of 30 mg to 60 mg, nor in the comparison of 60 mg to 90 mg. For this reason, the reviewers recommended that only the lowest dose level, 30 mg, should be approved for the indication of maintenance of healed erosive esophagitis. I concur with this decision.

Table 2: Rates (Percentage with 95% Confidence Intervals) for Maintenance of Healed EE at Month 6, ITT (table reproduced from Dr. Ruyi He's CDTL review)

	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	N=145	N=137		

			(b) (4)
Life-Table Rates	27.2 (18.3, 36.0)	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 Applicant prespecified a secondary endpoint for hierarchal analysis, percentage of 24-hour heartburn-free days. Dr. St. Amand noted in his clinical review that the percentage of 24-hour heartburn-free days was higher in patients treated with dexlansoprazole than with placebo. The percentage of 24-hour heartburn free days actually appeared to exceed the percentage of 24-hour heartburn-free days observed in the Applicant's GERD studies. (b) (4) (b) (4) The FDA has not included data on (b) (4) (b) (4) (b) (4) the CDTL and the biostatistical reviewers expressed concern about the validity of the comparison. They questioned the balance between study arms in symptom severity and rescue medication use, as well as the completeness of diary entries at both assessment times within each 24 hour period in each day. (b) (4)

Symptomatic GERD

The Applicant submitted the results from two randomized, double-blind, placebo-controlled studies that evaluated the effectiveness of multiple dose levels of dexlansoprazole (30 mg, 60 mg and 90 mg) for treatment of GERD. The studies were 4 weeks in duration. Daytime and nighttime symptoms were assessed in every 24 hour period with an electronic diary. The primary efficacy endpoint was relief of heartburn. The endpoint was reported as percentage of 24-hour periods without heartburn. To count as a heartburn free day, a patient had to have responded to at least one of the daytime or nighttime diary questions about presence of heartburn, and any response to the two questions in a 24 hour period had to be "no". One study (Study 137) evaluated 60 mg and 90 mg, and the other study (Study 082) evaluated 30mg and 60 mg.

In all dexlansoprazole dose levels studied, a significantly higher proportion of days without heartburn than placebo was observed. (See the table below, which is reproduced from Dr. Ruyi He's CDTL review.) The reviewers recommended that (b) (4), 30 mg, should be approved for this indication, and I concur. The Biostatistical reviewer noted in her review that although only a single study evaluated the dexlansoprazole 30 mg dose level, the efficacy observed in that study relative to placebo was highly statistically significant.

Table 3: Summary of Percentage of Days Without Heartburn (reproduced from Dr. Ruyi He's CDTL review)

	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)		

The Applicant proposed that the labeled indication should include the language, '(b) (4) (b) (4) There are 5 PPIs on the market, and (b) (4) includes this language in its indication. In this review, the reviewers re-examined what should constitute a diagnosis of (b) (4) and what evidence should be required to demonstrate that this entity has been adequately treated. Experts are unable to agree on an accepted definition of the entity (b) (4) (b) (4) The clinical reviewers evaluated the submitted data in the context of what is known about (b) (4) and symptoms and concluded that they could not justify diverging from what has been the standard approach to GERD labeling. Dr. St. Amand and Dr. He both concluded that the indication should be "treatment of heartburn associated with non-erosive GERD for 4 weeks".

In summary, the reviewers supported the approval of the lowest effective dose of dexlansoprazole studied for each of the 3 proposed indications – 60 mg for the healing of erosive esophagitis indication, 30 mg for the maintenance of healing of erosive esophagitis indication, and 30 mg for treatment of heartburn associated with non-erosive GERD. I agree with their recommendations.

8. Safety

The NDA submission included safety data from 5072 subjects who had been exposed to dexlansoprazole doses ranging from 30 mg to 300 mg. Of those subjects, 4548 were exposed to dexlansoprazole within the context of phase 3 studies. The duration of those studies ranged from 4 weeks to 6 months. Eight hundred sixty three patients were exposed to dexlansoprazole doses ranging 30-60 mg/day for ≥24 weeks, and 203 were exposed for ≥48 weeks.

There were 7 deaths in the safety data set. Six of the patients who died were treated with dexlansoprazole (5 treated with 60 mg and 1 treated with 90 mg). One of the patients was treated with lansoprazole (the racemic product). In contrast, there were no deaths in patients treated with placebo in the clinical trials. None of the deaths were considered treatment related by the investigators or Applicant. The causes of death included acute methadone toxicity, end stage liver disease, gastric cancer, acute promyelocytic leukemia, acute respiratory failure, sepsis related to elbow fracture repair, and liposuction surgery. Clinical Safety Reviewer Tamara Johnson, MD concluded in her review that there were no common associations among the deaths that implicated dexlansoprazole as the cause of death. I concur with her assessment.

Dr. Johnson was concerned by the higher total incidence of non-fatal SAEs in dexlansoprazole treated population than the lansoprazole or placebo populations in the safety data base. Of the 59 patients with SAEs among the 4548 total dexlansoprazole exposed patients, Dr. Johnson noted that SAEs most commonly occurred in the classes: infections, injury and nervous system disorders. Her greatest concern were imbalances in cardiovascular adverse events and injury events relative to placebo.

The following table, reproduced from Dr. Ruyi He's CDTL review, summarizes the number and rate per 100 patient months of exposure of nonfatal cardiovascular SAEs, including cardiac ischemic events, thrombotic events (deep venous thrombosis, pulmonary embolism and cerebral venous thrombosis), and a transient ischemic event (TIA). These data reveal no definitive pattern or dose response across the 3 ascending dexlansoprazole doses. In fact, the highest rate per 100 patient months occurs in the lowest dexlansoprazole dose and the lowest rate per 100 patient months occurs at the highest dose, 90 mg. The racemic product, lansoprazole, has a lower rate per 100 patient months than placebo, and the placebo rate per 100 patient months was similar to the rate observed in the highest dexlansoprazole dose level, 90 mg. The markedly smaller study population of the 30 mg dose group (N=455) relative to the other dexlansoprazole dose levels, lansoprazole arm and placebo arm probably contributed to the observation of an apparent higher risk of events associated with the lowest dose studied.

Table 4. Cardiovascular-Related Nonfatal Serious Adverse Events in All Phase 3 Studies

CARDIOVASCULAR-RELATED SAEs	**Treatment Group: n (rate per 100 PM)**					
	Placebo	**Dexlansoprazole**				**Lansop. 30 mg QD (N=1363) (Avg. PM=1.3)**
	(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)**	
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)**

The table totals of cardiovascular SAEs include events such as deep venous thrombosis (DVT), cerebral venous thrombosis, and pulmonary embolism. Please refer to detailed information provided in Section 7.3.4.1 and Tables 7.3.4.1.2 and 7.3.4.1.4 in Dr. Johnson's Clinical Safety review. Her review discusses all nonfatal cardiovascular events, includes narrative description of the serious cardiovascular events, and reports details of the Applicant's adjudication of cardiovascular adverse events by a cardiologist. It is clear from that review that events of chest pain were difficult to classify as ischemic in etiology. If the data in the table above are narrowed to the SAEs "ischemic CAD" (which are myocardial infarctions in the narrative review) and CAD NEC, there were a total of 2 events in the relatively small 30 mg dexlansoprazole group, 2 events in the 60 mg dexlansoprazole group, and 2 in the 90 mg group. Focusing on these ischemic cardiac events, the rate per 100 PM remains higher in the smaller 30 mg population, but the lack of a dose response in events persists and the total rate per 100 months exposure for the overall dexlansoprazole group drops to 0.05 (N=6), which is similar to the rate observed in placebo and lansoprazole 30 mg.

The events tabulated in the SAEs "ischemic CAD" and "CAD NEC" can be found in Dr. Tamara Johnson's safety review Table 7.3.4.1.2, which summarizes 9 Serious Cardiovascular events identified by the Applicant after the process of adjudication. In that table, all but one of the 6 dexlansoprazole events in the table above can be found listed as definitive cardiac events (2 in 30 mg, 2 in 60 mg and 1 in 90 mg). The specific subjects identified in Table 7.3.4.1.2 of Dr. Johnson's Clinical Review are:

Dexlansoprazole 30 mg:	Subject 32454009 (from GERD study)–Had MI (and CVA)
	Subject 9319002 (from GERD study)-Had MI and cardiogenic shock
Dexlansoprazole 60 mg:	Subject 32849038 (Healing EE study) – MI
	Subject 32957001 (Healing EE study) – CAD, NEC
Dexlansoprazole 90 mg:	Subject 18128038 (Maintenance EE study) – CAD

The second cardiac event in the dexlansoprazole 90 mg dose group in the Table above (from Dr. Ruyi He's review) cannot be identified in Table 7.3.4.1.2. Dr. Johnson's review Table 7.3.4.1.4, which lists her own adjudicated list of subjects with an adverse event she considered of cardiac etiology, reveals the dexlansoprazole 90 dose level Subject 30000009 (from a Healing of EE study), who was coded in the database as having ischemic coronary artery disorder due to arteriospasm or a cardiac arrhythmia.

The Office of Surveillance and Epidemiology was consulted regarding these data. Dr. Diane Wysowski concluded "It does not seem likely that dexlansoprazole is a cause of cardiovascular disorders in the clinical trial data." She was particularly persuaded by the lack of dose response and her review of the narratives associated with these events. She pointed out that the patients had confounding concomitant medical conditions that put them at risk for having these events, including hypertension, diabetes, and multivessel cardiovascular disease. She also noted that these events, which occurred relatively shortly after starting treatment, were associated with significant vascular disease. The majority of the events occurred within 2

months of starting treatment, and cardiac catheterization revealed extensive coronary disease. Some patients had stopped taking study medication a few days before onset of the event.

The cardiovascular findings from these clinical trials were presented at a CDER Regulatory Briefing. There was a strong consensus that these data did not constitute a signal of cardiovascular toxicity associated with dexlansoprazole. The lack of dose response, the lack of a plausible mechanism of action, the existence of predisposing concomitant medical conditions, and the very small overall number of patients in the treatment arm in which the events were observed (N=455) relative to the other arms were reasons given by the CDER officials to support their conclusions that the safety data did not constitute a safety signal. I concur with this assessment. Dr. Tamara Johnson recommended that the cardiovascular events should be included in product labeling, and myocardial infarction has been listed with the adverse events observed in the clinical trials section of the label.

With regard to the injury-related serious adverse events, which are summarized in the table below (reproduced from Dr. Ruyi He's CDTL review), these events only occurred in dexlansoprazole treated patients in the clinical trials. Pooled incidence rates did appear to increase with increasing dexlansoprazole dose. Note, however, that these events are non-specific or soft tissue related. There were only 3 categories of fracture, each a single event – ankle (1), rib (1) and "upper limb fracture" (1). In fact, the events captured in the table below are not clearly "injuries" per se, e.g. fall, syncope, vertigo positional. Eight of the 19 events in the table could be included in this latter category. The clinical reviewers were concerned about these events because they questioned whether the injuries might be occurring because of altered mental status or balance. However, they were unable to establish that this was in fact an etiologic factor upon review of narratives. Reports in the literature suggest that proton pump inhibitors might be associated with higher risk for hip fractures, which may be related to altered calcium absorption due to elevated gastric pH. Hip fractures and vertebral fractures that might be associated with osteopenia, however, were not observed in this safety database.

Table 5: Injury-Related Nonfatal Serious Adverse Events in All Phase 3 Studies (reproduced from Dr. Ruyi He's CDTL review)

INJURY-RELATED SAEs	Treatment Group: n (rate per 100 PM)					
	Placebo	Dexlansoprazole MR				Lansoprazole
		30 mg QD	60 mg QD	90 mg QD	Total	30 mg QD
	(N=896) (Avg. PM=1.2)	(N=455) (Avg. PM=2.1)	(N=2311) (Avg. PM=2.3)	(N=2142) (Avg. PM=2.8)	(N=4548) (Avg. PM=2.7)	(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

INJURY-RELATED SAEs	Treatment Group: n (rate per 100 PM)					
	Placebo	Dexlansoprazole MR				Lansoprazole
		30 mg QD	60 mg QD	90 mg QD	Total	30 mg QD
	(N=896) (Avg. PM=1.2)	(N=455) (Avg. PM=2.1)	(N=2311) (Avg. PM=2.3)	(N=2142) (Avg. PM=2.8)	(N=4548) (Avg. PM=2.7)	(N=1363) (Avg. PM=1.3)
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.

The "injury" data were also presented to the CDER Regulatory Briefing. There was consensus that these data do not constitute a specific safety signal. The discussants at the regulatory briefing suggested that if there has been concern raised by reports in the literature regarding the impact of PPIs on calcium homeostasis and bone integrity, the reviewers should consider a post marketing study to evaluate this. I concur with this assessment and recommendation.

9. Advisory Committee Meeting/Regulatory Briefing

There was no advisory committee meeting for this application. The product is not a new molecular entity. It is the R-enantiomer of a product that was approved in 1995. There were no questions to take to an Advisory Committee meeting.

As discussed above in Section 8 Safety, adverse events that concerned the clinical reviewers were taken to a CDER Regulatory Briefing for discussion and recommendations. The briefing panel, which was composed of CDER senior management officials, did not consider that the apparent imbalance in overall cardiovascular events and "injuries" (see more detailed discussion above) constituted safety signals. CDER staff reviewers from multiple disciplines were present and contributed to the discussion. Please refer to the CDTL review by Dr. Ruyi He for a list of the questions that the Regulatory Briefing panel was asked to address after the safety data had been presented and discussed in detail.

10. Pediatrics

The Applicant's pediatric assessment plan was presented to the PeRC. The requirement for a pediatric study for ages birth to less than one month will be waived for the following indications: healing and maintenance of healing of all grades of erosive esophagitis and heart burn associated with non-erosive GERD. This is because the necessary studies are impossible or highly impractical. The pediatric study requirement will also be waived for ages 1-11 months for the following indications: healing and maintenance of healing of all grades of erosive esophagitis. This is because the necessary studies are impossible or highly impractical. The number of pediatric patients with erosive esophagitis in this age group would be limited.

The Applicant will be required to conduct the following studies:

1. Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 1 year to 11 years.

   Final report submission: October 31, 2013

2. Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 12 years to 17 years.

   Final report submission: March 31, 2013

3. Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 month to 11 months.

   Final report submission: July 31, 2016

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

   Final report submission: October 31, 2013

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

   Final report submission: March 31, 2013

11. Other Relevant Regulatory Issues

Three sites were inspected by DSI and DSI concluded that none of the violations detected at the sites affected the validity of data. The data from the sites were not excluded from the evaluation of this NDA.

Dr. St. Amand noted in his review that the applicant certified that no investigator had a proprietary interest in dexlansoprazole or a significant equity interest in the sponsor.

12. Labeling

The applicant's proposed product name, Kapidex, was found acceptable by the tradename review team.

Please refer to Section 5 Clinical Pharmacology, Section 7 Efficacy, and Section 8 Safety of this review for a more detailed discussion of labeling issues that were identified during the course of the clinical review.

The Division incorporated the labeling suggestions from the Maternal Health Team Review.

The reviewers determined that there is no reason to require a Medication guide at this time.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

I concur with the reviewers' recommendation that Kapidex 30 mg should be approved for treatment of heartburn associated with GERD and for maintenance of healing of erosive esophagitis. I concur with the reviewers' recommendation that Kapidex 60 mg should be approved for the single indication, "healing of all grades of erosive esophagitis". I agree with their decision that Kapidex(b) (4) should not be approved.

- Risk Benefit Assessment

I concur with the reviewers that because the(b) (4) Kapidex doses provide no additional benefit compared to Kapidex 30 mg for treatment of heartburn associated with GERD and for maintaining healing of erosive esophagitis that there is no justification for approval of the two(b) (4) doses,(b) (4) for those indications. Similarly, for healing erosive esophagitis, because there is no additional benefit associated with the(b) (4) Kapidex dose,(b) (4) relative to the (b) (4) dose studied, 60 mg, there is no justification for approving the(b) (4) dose for that indication.

I concur that the adverse event profile in the large safety data base submitted in this NDA did not provide evidence that there is a new risk associated with this R-enantiomer of the previously approved racemic lansoprazole. The safety data were thoroughly evaluated and discussed during the review process, including with review staff from OSE and in a CDER Regulatory Briefing. I concur that the risk benefit profile demonstrated in this NDA support the approval of Kapidex 30 mg and Kapidex 60mg.

- Recommendation for Postmarketing Risk Management Activities

Not applicable.

- Recommendation for other Postmarketing Study Commitments

I concur with the reviewers' recommendation that the applicant be required to conduct a postmarketing clinical trial to evaluate the impact of dexlansoprazole on calcium homeostasis and bone integrity. The reason for conducting this trial is to assess a potential serious risk of bone fractures in patients who have prolonged use and/or higher doses of Kapidex (dexlansoprazole) Delayed Release Capsules.

The Applicant will conduct the following postmarketing clinical trial, pursuant to section 505(o)(3) of the FDCA:

> A clinical trial to evaluate the effect of Kapidex (dexlansoprazole) Delayed Release Capsules on bone homeostasis. The primary endpoint will be biomarkers of bone formation and bone resorption. Treatments will include: placebo, dexlansoprazole and esomeprazole.

The timetable for submission is:

Final protocol Submission:	August 31, 2009
Trial Start Date:	October 31, 2009
Final Report Submission:	December 31, 2011

The Applicant will also be required to conduct the following pediatric studies under PREA:

1. Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 1 year to 11 years.

   Final report submission: October 31, 2013

2. Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 12 years to 17 years.

   Final report submission: March 31, 2013

3. Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 month to 11 months.

   Final report submission: July 31, 2016

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

   Final report submission: October 31, 2013

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

   Final report submission: March 31, 2013

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/s/

Donna Griebel
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DIRECTOR