

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-287**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Submission Number	22-287
Submission Code	000
Letter Date	31 December 2007
Stamp Date	31 December 2007
PDUFA Original Goal Date	31 October 2008
PDUFA Extended Goal Date	31 January 2009
Reviewer Name	Tamara Johnson, MD, MS
Review Completion Date	22 December 2008
Established Name	Dexlansoprazole
(Proposed) Trade Name	KAPIDEX
Therapeutic Class	Proton pump inhibitor
Applicant	TAP Pharmaceutical Products, Inc
Priority Designation	Standard
Formulation	Oral delayed release capsules
Dosing Regimen	30mg, 60mg, (b) (4) daily
Indication	Healing of Erosive Esophagitis, Maintenance of Healed Erosive Esophagitis, and Symptomatic Gastroesophageal Reflux Disease
Intended Population	Adults 18 and older

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>4</b>
1.1	Recommendation on Regulatory Action.....	4
1.2	Risk Benefit Assessment .....	4
1.3	Recommendations for Postmarketing Risk Management Activities .....	5
1.4	Recommendations for other Post Marketing Study Commitments .....	5
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND.....</b>	<b>5</b>
2.1	Product Information.....	5
2.2	Tables of Currently Available Treatments for Proposed Indications.....	6
2.3	Availability of Proposed Active Ingredient in the United States.....	8
2.4	Important Safety Issues with Consideration to Related Drugs .....	8
2.5	Summary of Pre-submission Regulatory Activity Related to Submission .....	12
2.6	Other Relevant Background Information .....	12
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>12</b>
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....</b>	<b>13</b>
<b>5</b>	<b>SOURCES OF CLINICAL DATA .....</b>	<b>13</b>
5.1	Tables of Clinical Studies.....	13
5.2	Review Strategy.....	13
5.3	Discussion of Individual Studies .....	13
<b>6</b>	<b>REVIEW OF EFFICACY.....</b>	<b>13</b>
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>13</b>
7.1	Methods .....	17
7.1.1	Clinical Studies Used to Evaluate Safety.....	17
7.1.2	Adequacy of Data .....	21
7.1.3	Pooling Data Across Studies to Estimate and Compare Incidence.....	21
7.2	Adequacy of Safety Assessments .....	22
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	22
7.2.2	Explorations for Dose Response.....	26
7.2.3	. Special Animal and/or In Vitro Testing.....	26
7.2.4	. Routine Clinical Testing .....	26
7.2.5	. Metabolic, Clearance, and Interaction Workup .....	27
7.2.6	. Evaluation for Potential Adverse Events for Similar Drugs in Drug Class .....	27
7.3	Major Safety Results .....	27
7.3.1	Deaths .....	27
7.3.2	Nonfatal Serious Adverse Events .....	29
7.3.3	Dropouts and/or Discontinuations .....	34
7.3.4	Significant Adverse Events.....	38
7.3.5	Submission Specific Primary Safety Concerns.....	52
7.4	Supportive Safety Results.....	52
7.4.1	Common Adverse Events .....	52
7.4.2	Laboratory Findings.....	57
7.4.3	Vital Signs .....	59
7.4.4	Electrocardiograms (ECGs).....	59
7.4.5	Special Safety Studies.....	59
7.4.6	Immunogenicity .....	61
7.5	Other Safety Explorations .....	61

7.5.1	Dose Dependency for Adverse Events.....	61
7.5.2	Time Dependency for Adverse Events .....	61
7.5.3	Drug-Demographic Interactions .....	61
7.5.4	Drug-Disease Interactions.....	64
7.5.5	Drug-Drug Interactions.....	64
7.6	Additional Safety Explorations.....	65
7.6.1	. Human Carcinogenicity .....	65
7.6.2	. Human Reproduction and Pregnancy Data.....	65
7.6.3	Pediatrics and Effect on Growth.....	66
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	66
7.7	Additional Submissions.....	66
<b>8</b>	<b>POSTMARKETING EXPERIENCE.....</b>	<b>66</b>
8.1	Cardiovascular Risk.....	67
8.2	Hip Fracture and Calcium Homeostasis .....	67
8.3	Hepatic Enzyme Abnormalities/Cholestatic Disorders/Pancreatitis .....	68
8.4	Gastric Polyps.....	68
8.5	Upper Respiratory Tract Infections .....	68
8.6	Lower Respiratory Tract Infections.....	68
8.7	Anemia .....	69
8.8	Clostridium difficile-associated Diseases.....	69
<b>9</b>	<b>APPENDICES .....</b>	<b>69</b>
9.1	Literature Review/References .....	92
9.2	Labeling Recommendations .....	92
9.3	Regulatory Briefing.....	104

*The following review and recommendations are based primarily on examination of the clinical safety data provided in this application. For the review of efficacy, please see Dr. Keith St. Amand's review of this application.*

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

For Dexlansoprazole capsules, at doses of 30mg and 60mg daily for the Healing of Erosive Esophagitis, Maintenance of Healed Erosive Esophagitis, and Symptomatic Gastroesophageal Reflux Disease (GERD) treatment in adult patients, approval is recommended.

**Approved Doses of Dexlansoprazole**

<b>Indication</b>	<b>Dosage</b>
Healing of Erosive Esophagitis	60mg daily
Maintenance of Healed Erosive Esophagitis	30mg daily
Symptomatic GERD	30mg daily

The 90mg dose of dexlansoprazole did not provide additional benefit compared to 60mg for Healing of Erosive Esophagitis, as the 60mg dose of dexlansoprazole did not provide additional benefit compared to 30mg for Maintenance of Healed Erosive Esophagitis. Additionally, due to potential safety risks of fracture/injury-related adverse events, it is recommended that the sponsor conduct postmarketing studies to better elucidate if such risks exist.

### 1.2 Risk Benefit Assessment

Dexlansoprazole belongs to the drug class of proton pump inhibitors (PPI); a class which now houses 5 marketed products. (See section 2.2.) Throughout its Phase 3 development program, dexlansoprazole has demonstrated greater benefit for the symptomatic GERD and erosive esophagitis patient populations when compared to placebo and lansoprazole 30mg. Although, as discussed in the efficacy review by Dr. St. Amand, dexlansoprazole provides no 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 30mg 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. Labeling recommendations have been advised to address this potential concern. This reviewer, however, remains with concern for fracture/injury-related adverse events, which occurred at greater incidence with dexlansoprazole than its comparators. (See section 7 Safety Summary) In order to manage this potential risk, a postmarketing study and labeling recommendations are advised.

### 1.3 Recommendations for Postmarketing Risk Management Activities

The proposed study design for postmarketing studies to explore the potential safety risk of fracture/injury-related adverse events will be evaluated and finalized by the Division's Safety Team.

No serious risks have been identified in clinical trials with dexlansoprazole; therefore, routine measures will apply and include provision of the full prescribing information, a patient package insert, and routine pharmacovigilance activities.

### 1.4 Recommendations for other Post Marketing Study Commitments

Other than a commitment to conduct deferred pediatric studies, there are no other recommendations for postmarketing study commitments.

## 2 Introduction and Regulatory Background

Dexlansoprazole seeks to treat the clinical conditions of gastroesophageal reflux disease (GERD) and erosive esophagitis (EE). Both of these conditions result from the frequent reflux of acidic stomach contents up into the esophagus. EE, however, distinguishes itself by the formation of painful erosions and ulcerations in the esophageal mucosa, and is diagnosed by endoscopy. In the US, reflux affects approximately 20% of adults weekly and 10% of adults daily, with 50% of those affected developing mucosal damage.<sup>1</sup> EE leads to more severe complications, such as dysphagia, strictures, esophageal metaplasia (Barrett's esophagus), and adenocarcinoma. Where GERD may be treated with antacids, H<sub>2</sub>-receptor antagonists, and short-term PPI use, treatment of EE requires more intense and long-term treatment with PPI's.

TAP has developed Dexlansoprazole and seeks to demonstrate its use in treating GERD symptoms, healing erosive esophagitis (EE) and maintaining healed EE.

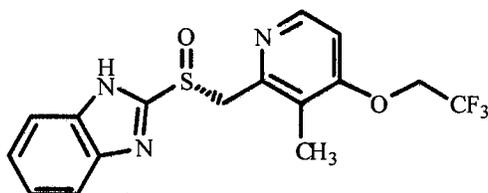
### 2.1 Product Information

**Product Name:** Dexlansoprazole  
**Proposed Trade Name:** KAPIDEX  
**Pharmacological Class:** Proton Pump Inhibitor (PPI)

#### **Chemical structure of Dexlansoprazole:**

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<sup>1</sup> Gastroesophageal Reflux Disease. Chapter 14. Gastrointestinal Disorders - *Kenneth R. McQuaid, MD*. CURRENT MEDICAL DIAGNOSIS & TREATMENT - 47th Ed. (2008). Lange Medical Books/McGraw-Hill, Medical Publishing Division: New York. <http://online.statref.com/document.aspx?fxid=27&doid=194>



Chemical Name: (+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole  
 Chemical Formula: C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S  
 Molecular Weight: 369.36

Dexlansoprazole, a newly developed proton pump inhibitor from TAP Pharmaceuticals, is the *R*-enantiomer of lansoprazole. Dexlansoprazole has shown a superior pharmacokinetic and pharmacodynamic profile compared to that of the *S*-enantiomer of lansoprazole. It is formulated as a dual-delayed release capsule consisting of two granules, a fast-release granule (within first hour) and a slow-release granule (within 4-5 hours), designed to provide extended pharmacological activity. Dexlansoprazole acts by blocking the (H<sup>+</sup>, K<sup>+</sup>)-ATPase (proton) pumps of parietal cells of the stomach. This action suppresses acidic secretions, raises the pH of the stomach, and subsequently decreases damage to the esophageal mucosa during episodes of acid reflux.

TAP Pharmaceuticals is seeking the following indications for Dexlansoprazole:

Indication	Recommended Dose	Frequency
Healing (b) (4) of all grades of EE	60 mg (b) (4) capsule	Once daily for up to 8 weeks
Maintenance of healed EE (b) (4)	30 mg (b) (4) capsule	Once daily*
Treating (b) (4) heartburn (b) (4) associated with GERD	30 mg capsule	Once daily for 4 weeks

\*Controlled studies did not extend beyond 6 months.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are numerous products currently marketed to treat the three proposed indications. The table below lists only prescription products for oral administration. Also available for relief of GERD symptoms are various over-the-counter H<sub>2</sub>-receptor antagonists, antacids, antacid/H<sub>2</sub>-receptor antagonist combination products, and for treatment of GERD symptoms, Prilosec OTC.

**Table 2.2.1. Available Prescription Products for Treatment of Proposed Indications**

<b>DRUG CLASS</b>	<b>Approval Date</b>	<b>Indications*</b>
<b>Proton pump inhibitors</b>		
PRILOSEC (omeprazole) Delayed-Release Tablets 10mg/20mg/40mg cap (AstraZeneca)	9/1989	<b>HEE 20 mg QD for 4–8 wks</b> <b>Maintenance of HEE 20 mg QD</b> <b>sGERD 20 mg QD for 4 wks</b> <b>(Peds ≥2, &gt;20kg) HEE/sGERD 20mg QD</b> <b>(Peds ≥2, ≤20kg) HEE/sGERD 10mg QD</b>
PREVACID (lansoprazole) Delayed-Release Tablets 15mg/30mg cap, 15mg/30mg disintegrating tab (TAP Pharmaceuticals)	5/1995	<b>HEE 30 mg QD for up to 8 wks</b> <b>Maintenance of HEE 15 mg QD</b> <b>GERD 15mg QD up to 8wks</b> <b>(Peds 12-17) HEE 30mg QD up to 8wks</b> <b>(Peds 12-17) sGERD 15mg QD up to 8wks</b> <b>(Peds 1-11, &gt;30kg) HEE/sGERD 30mg QD 12wks</b> <b>(Peds 1-11, ≤30kg) HEE/sGERD 15mg QD 12wks</b>
ACIPHEX (rabeprazole sodium) Delayed-Release 10mg/20mg tab (Eisai Medical Res/PriCara)	8/1999	<b>HEE 20 mg QD for 4–8 wks</b> <b>Maintenance of HEE 20 mg QD</b> <b>sGERD 20 mg QD for 4 wks</b>
PROTONIX (pantoprazole sodium) Delayed-Release Tablets 20mg/40mg (Wyeth-Ayerst Lab)	2/2000	<b>HEE 40 mg QD for 8 wks</b> <b>Maintenance of HEE 40 mg QD</b> <b>GERD 40 mg IV QD for 7-10 days</b>
NEXIUM (esomeprazole) Delayed-Release 20mg/40mg cap (AstraZeneca)	2/2001	<b>HEE 20 mg-40mg QD for 4–8 wks</b> <b>Maintenance of HEE 20 mg QD for 6 mo.</b> <b>GERD 20 mg QD for 4 wks</b> <b>(Peds 12-17) GERD 20-40 mg QD up to 8wks</b>
ZEGERID (omeprazole) Powder 20mg/40mg packet (Santarus)	6/2004	<b>HEE 20 mg QD for 4–8 wks</b> <b>Maintenance of HEE 20 mg QD</b> <b>GERD 20 mg QD for 4 wks</b>
<b>H<sub>2</sub>-receptor antagonists</b>		
TAGAMET (Cimetidine) 300mg/400mg/800mg tab, 300mg/5ml sol'n (GSK)	8/1977	<i>For &gt;16 y.o.</i> <b>GERD 800mg BID or 400mg QID for 12 wks</b>
ZANTAC (Ranitidine) 150mg/300mg tab, 25mg/150mg effervescent tab, 15mg/ml syrup (GSK)	6/1983	<b>HEE 150mg QID</b> <b>Maintenance of HEE 150mg BID</b> <b>GERD 150mg BID</b> <b>(Peds) HEE/GERD 2.5-5mg/kg BID</b>
PEPCID (Famotidine) 20mg/40mg tab, 20mg/40mg disintegrating tab, 40mg/5ml susp	10/1986	<b>HEE 20 mg-40mg BID up to 12 wks</b> <b>GERD 20 mg BID for 6 wks</b> <b>(Peds) HEE/GERD 0.5mg/kg BID</b>

DRUG CLASS	Approval Date	Indications*
AXID (Nizatidine) 150mg/300mg cap, 15mg/ml sol'n (Reliant)	4/1988	GERD 150mg BID up to 12 wks (Peds) HEE/GERD 150mg BID up to 8 wks

\*HEE: healing of erosive esophagitis; sGERD: symptomatic GERD

Source: PDR Monthly Prescribing Guide. Thomson Healthcare, Montvale, NJ. Dec 2007, 4(4):167-174.

### 2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient of Dexlansoprazole, *R-lansoprazole*, is currently marketed in the United States in a 1:1 racemic mixture with *S-lansoprazole* as lansoprazole (Prevacid®). Initially approved in the US on May 10, 1995, lansoprazole has been approved in 97 countries and consumed by an estimated 432 million persons. Although lansoprazole has been marketed worldwide, Dexlansoprazole has never been approved or marketed. The active ingredient, *R-lansoprazole*, is not available in isolation, only as a component of the mixture, lansoprazole.

### 2.4 Important Safety Issues with Consideration to Related Drugs

Important issues surrounding PPI use in the literature are varied. Most reports cite that reduced stomach acidity causes poor absorption of iron, calcium, and vitamin B12 leading to nutritional deficiencies; bacterial colonization in the GI tract leading to enteric infections; hypersecretion of gastrin leading to carcinogenesis; and rebound acid secretion post PPI discontinuation leading to dependency on the anti-secretory drugs (Schubert et al. 2008, Cote et al 2008). More recent reports discuss the increasing incidence of hip fractures with duration of PPI therapy >7 years (Targownik et al. 2008, Yang et al. 2006) and serious cardiovascular risk with concomitant use of PPIs and clopidogrel (Gilard et al. 2008, Pezalla et al. 2008).

Currently labeling acknowledges common adverse reactions such as headache, diarrhea, abdominal pain, nausea, flatulence, URI, dizziness, vomiting, rash, constipation, cough, dry mouth, asthenia, back pain, eructation, insomnia, and hyperglycemia. PPIs have also been reported to increase INR and prothrombin time when administered concomitantly with warfarin. Additionally, within the healthcare community, PPIs have been associated with elevated liver enzymes or abnormal liver function tests. Anaphylactic/anaphylactoid reactions, hepatic failure ± jaundice, anemias and other hematologic derangements have been documented in postmarketing reports. Table 2.4.1. details labeled safety issues by specific PPI.

**Table 2.4.1. Safety Issues with Proton Pump Inhibitors**

Drug Name	Common Adverse Events	Drug Interactions	Postmarketing AE's
PRILOSEC (omeprazole) NDA 019810 4/27/2007 label	Headache Diarrhea Abdominal Pain Nausea URI Dizziness Vomiting Rash Constipation Cough Asthenia Back Pain	Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Although in normal subjects no interaction with theophylline or propranolol was found, There have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (e.g., cyclosporine, disulfiram, and benzodiazepines). Omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). Concomitant administration has been reported to reduce the plasma levels of atazanavir, and may increase the serum levels of tacrolimus.	Not available.
PREVACID (lansoprazole) NDA 020406 6/14/2007 label	Diarrhea Abdominal Pain Constipation Nausea	<b>Theophylline – increased clearance of theo;</b> <b>Warfarin – possible increased INR,</b> <b>Prothrombin time;</b> May interfere with absorption of drugs where gastric pH determines bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin)	<i>Body as a Whole</i> – anaphylactic/anaphylactoid reactions; <i>Digestive System</i> - hepatotoxicity, pancreatitis, vomiting; <i>Hemic and Lymphatic System</i> - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; <i>Musculoskeletal System</i> - myositis; <i>Skin and Appendages</i> – <b>severe dermatologic reactions</b> including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); <i>Special Senses</i> - speech disorder; <i>Urogenital System</i> – interstitial nephritis, urinary retention.

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPIDEX (Dexlansoprazole)

Drug Name	Common Adverse Events	Drug Interactions	Postmarketing AE's
ACIPHEX (rabeprazole sodium) NDA 021456 11/08/2002 label	Headache	Rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). Steady state interactions of rabeprazole and other drugs metabolized by this enzyme system have not been studied in patients. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly.	Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angioedema, bullous and other drug eruptions of the skin, interstitial pneumonia, interstitial nephritis, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported. Increases in prothrombin time/INR in patients treated with concomitant warfarin have been reported.
PROTONIX (pantoprazole sodium) NDA 020987 5/5/2004 label	Headache Diarrhea Flatulence Abdominal pain Rash Eructation Insomnia Hyperglycemia	No dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam, (and its active metabolite, desmethyldiazepam), diclofenac, naproxen, piroxicam, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin (see below), midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. No interaction with concomitantly administered antacids.	There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including pantoprazole, and warfarin concomitantly. Spontaneous reports include anaphylaxis (including anaphylactic shock); angioedema ( <b>Quincke's edema</b> ); <b>anterior ischemic optic neuropathy</b> ; elevated CPK (creatine phosphokinase), severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; interstitial nephritis; pancreatitis; pancytopenia; and rhabdomyolysis. In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPIDEX (Dexlansoprazole)

Drug Name	Common Adverse Events	Drug Interactions	Postmarketing AE's
NEXIUM (esomeprazole) NDA 021153 4/27/2007 label	Diarrhea Headache Abdominal Pain Nausea Flatulence Constipation Dry mouth	Concomitant administration may decrease diazepam clearance by 45%, and reduce plasma levels of atazanavir. May interfere with absorption of drugs where gastric pH determines bioavailability (e.g., ketoconazole, iron salts, digoxin).	Post-marketing reports of changes in prothrombin measures among patients on concomitant warfarin therapy. Other reported events include: <i>Blood And Lymphatic System Disorders:</i> agranulocytosis, pancytopenia; <i>Eye Disorders:</i> blurred vision; <i>Gastrointestinal Disorders:</i> pancreatitis; stomatitis; <i>Hepatobiliary Disorders:</i> hepatic failure, hepatitis with or without jaundice; <i>Immune System Disorders:</i> anaphylactic reaction/shock; <i>Infections and Infestations:</i> GI candidiasis; <i>Musculoskeletal And Connective Tissue Disorders:</i> muscular weakness, myalgia; <i>Nervous System Disorders:</i> hepatic encephalopathy, taste disturbance; <i>Psychiatric Disorders:</i> aggression, agitation, depression, hallucination; <i>Renal and Urinary Disorders:</i> interstitial nephritis; <i>Reproductive System and Breast Disorders:</i> gynecomastia; <i>Respiratory, Thoracic and Mediastinal Disorders:</i> bronchospasm; <i>Skin and Subcutaneous Tissue Disorders:</i> alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN, some fatal).
ZEGERID (omeprazole) NDA 021849 12/21/2007 label	Headache Diarrhea Abdominal Pain Nausea URI Dizziness Vomiting Rash Constipation Cough Asthenia Back Pain	Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, and benzodiazepines). Omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). Concomitant administration has been reported to reduce the plasma levels of atazanavir, and may increase the serum levels of tacrolimus. Co-administration of omeprazole and clarithromycin have resulted in increases of plasma levels of omeprazole, clarithromycin	Atrophic gastritis

\*Data obtained from Drugs@FDA website, U.S. Food and Drug Administration .  
[www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). Updated Daily.

## 2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Between 2004 and 2007, representatives from TAP Pharmaceuticals Inc. (TAP) met and corresponded with the Agency regarding the development program for Dexlansoprazole capsules.

- The original IND (#69,927) for Dexlansoprazole was submitted to the Agency on May 28, 2004.
- On July 27, 2004, the sponsor requested a Type C Meeting to discuss the development program and investigational plan. This included a plan for progressing directly from Phase 1 studies to Phase 3 studies, a recommendation for two pivotal clinical trials per proposed indication, and request of a rationale for only using the 90mg dose of Dexlansoprazole in studies. Meeting held October 6, 2004.
- On March 4, 2005, an End-of-Phase II meeting was requested between the Agency and the sponsor (TAP) to discuss acceptability of proceeding to Phase 3 with the product and the acceptability of your proposed Phase 3 program. As TAP proposed use of 60mg and 90mg doses of Dexlansoprazole in their Phase 3 program, the Agency reminded the sponsor that they would need to provide justification of these high dosages in their planned NDA and demonstrate an acceptable safety profile. Meeting held May 12, 2005.
- On December 22, 2005, a Type C meeting was requested between the Agency and the sponsor to discuss an amendment to the ongoing non-erosive GERD and maintenance of healing of EE studies to include a 30-mg dosage regimen in the Phase 3 program, and the design of a planned warfarin drug interaction study. Meeting held March 1, 2006.
- On April 19, 2006, the sponsor requested a Type B meeting to discuss CMC and Clinical Pharmacological issues. Meeting held June 22, 2006.
- On June 20, 2007, the sponsor requested a Type B meeting to discuss CMC and Clinical Pharmacology issues. Meeting held August 23, 2007. TAP submitted additional information dated September 26, 2007, requested by FDA at the meeting. FDA and TAP had a follow-up teleconference on November 27, 2007.
- On June 18, 2007, the sponsor requested a Type B meeting to discuss Regulatory, Non-clinical and Clinical development program issues. Meeting held October 1, 2007.
- On August 13, 2007, the sponsor requested a Type C meeting to discuss the proposed pediatric assessment plan for Dexlansoprazole. Meeting held November 2, 2007.
- The NDA was submitted to the Agency on December 28, 2007.

## 2.6 Other Relevant Background Information

There is no additional relevant background information.

## 3 Ethics and Good Clinical Practices

***For section 3, please refer to Dr. St. Amand's review.***

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

***For section 4, please refer to Dr. St. Amand's review.***

## **5 Sources of Clinical Data**

The sources of clinical data evaluated for this safety review are 6 well-controlled randomized studies and one uncontrolled open-label study conducted by the sponsor. These studies were multicenter studies conducted at US sites (50%) and non-US sites (50%): Australia, Bulgaria, Canada, Colombia, Czech Republic, Estonia, Germany, Hungary, India, Israel, Latvia, Lithuania, New Zealand, Peru, Poland, Russia, Slovakia, South Africa, and Ukraine.

### **5.1 Tables of Clinical Studies**

***For section 5.1, please refer to Dr. St. Amand's review.***

### **5.2 Review Strategy**

This application was submitted in electronic CTD format. The clinical section included study protocols, efficacy reports and safety reports for seven Phase III clinical studies: 6 controlled efficacy/safety studies and one open-label long-term safety study. The clinical review of this application is shared between Dr. St. Amand, who completed the efficacy review, and this medical officer, who completed the safety review. **This reviewer's final judgment on safety** for the proposed indications is based on the safety profile demonstrated in this application and published medical literature relevant to the drug class.

### **5.3 Discussion of Individual Studies**

Discussion of individual safety studies is provided in Section 7.1.1. of the Review of Safety.

## **6 Review of Efficacy**

***For section 6, please refer to Dr. St. Amand's efficacy review.***

## **7 Review of Safety**

## Safety Summary

The safety assessment for this new drug application for Dexlansoprazole (KAPIDEX) 30mg, 60mg, (b) (4) daily, for healing (b) (4) of all grades erosive esophagitis (EE), maintaining healed EE (b) (4), and treating heartburn (b) (4) associated with gastroesophageal reflux disease (GERD), examines ~6,000 patients who have received  $\geq 1$  dose of Dexlansoprazole. The safety assessment reviews six well-controlled Phase 3 studies (two per proposed indication), one ongoing Phase 3 open-label long-term study, and sixteen Phase 1 studies. The demonstrated safety profile for Dexlansoprazole in Phase 3 studies was acceptable when compared to lansoprazole 30mg and placebo. However, there was concern regarding dexlansoprazole on the following issues:

- increased risk of adverse events (§7.4.1)
- increased risk of nonfatal serious events (§7.3.2)
- increased risk of cardiovascular adverse events in 30mg Dexlansoprazole (§7.3.4.1)
- increased risk of injury-related adverse events (§7.3.4.2)

**Table of Overall Safety Concerns with Dexlansoprazole**

<i>Subjects (updated @4 mos.)</i>	<b>Treatment Groups: n (%)</b>					
	<b>Placebo (N=896)</b>	<b>Dex 30mg (N=455)</b>	<b>Dex 60mg (N=2311)</b>	<b>Dex 90mg (N=2142)</b>	<b>Total Dex (N=4548)</b>	<b>Lanso (N=1363)</b>
<b>AE's</b>	260 (29%)	175 (38.5%)	874 (37.8%)	782 (36.5%)	1758 (38.7%)	380 (27.9%)
<b>Deaths</b>	0 (0%)	0 (0%)	5 (<0.01%)	1 (<0.01%)	6 (<0.01%)	1 (<0.01%)
<b>Nonfatal SAE's</b>	2 (0.2%)	4 (0.9%)	26 (1.1%)	29 (1.4%)	59 (1.3%)	7 (0.5%)
<b>AE leading to D/C</b>	41 (4.6%)	9 (2%)	78 (3.4%)	77 (3.6%)	164 (3.6%)	18 (1.3%)

Among all adverse events (AE) in the Phase 3 Dexlansoprazole studies, the Dexlansoprazole treatment group had a 10% higher risk of AE than placebo or lansoprazole treatment group. However, there was no dose-dependent trend. The most frequently reported ( $\geq 1$  subject/100 PM) adverse events were Diarrhea (Excl Infective); Upper Respiratory Tract Infections; Gastrointestinal and Abdominal Pains (Excl Oral and Throat); Nausea and Vomiting Symptoms; Headaches NEC; and Flatulence, Bloating and Distension. These common adverse events were similar to currently marketed PPIs.

There were seven deaths reported in all Phase 3 studies. Five occurred in subjects taking dexlansoprazole 60mg, 1 occurred in a patient taking dexlansoprazole 90mg, and 1 occurred in a patient taking lansoprazole 30mg. None were considered related to the study drug.

Nonfatal Serious Adverse Events (SAE) occurred in 68 subjects in all the Phase 3 studies. SAE risk was the highest for Dexlansoprazole (Dex) treatment groups, showing ~3x higher risk of SAE in Dex vs. lansoprazole and 6x risk in Dex vs. placebo. There was no dose-response trend seen with Dex. The most represented MedDRA system organ classes (SOC) were Infections, Injury, and Nervous System Disorders. There was no pattern or trend observed among SOC of Infections and Nervous System Disorders, however, Injury required further review. Eleven SAEs were considered possibly related to the study drug. One event occurred on 60mg Dexlansoprazole, 8 events on 90mg Dexlansoprazole, and 2 events on 30mg lansoprazole.

Evaluation of SAEs by incidence rates again demonstrates the highest incidence with Dex treatment groups. The table below highlights imbalances that raise concern in the SOC of Cardiovascular, Injury, and Infection. The Dex incidence, however, among SOC Cardiovascular did not reveal a dose-related trend and among SOC Infection was similar between dexlansoprazole and lansoprazole.

**Table of Specific Nonfatal SAEs of Concern**

MedDRA SOC	Treatment Group: n (rate per 100 PM)					
	Placebo (N=896) Avg PM=1.2	Dexlansoprazole				Lansoprazole 30 mg QD (N=1363) Avg PM=1.3
		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)	
Total Exposure in Patient-Mos.	1075.2	955.5	5315.3	5997.6	12279.6	1771.9
Total Subjects w/ ≥ 1 SAE	2 (0.19)	4 (0.43)	26 (0.49)	29 (0.48)	59 (0.48)	7 (0.39)
Cardiovascular	1 (0.09)	4 (0.43)	9 (0.17)	5 (0.08)	18 (0.15)	1 (0.06)
Injuries	0	0	6 (0.11)	15 (0.25)	21 (0.17)	0
Infections	0	1 (0.11)	13 (0.24)	6 (0.10)	20 (0.16)	3 (0.17)

There were 983 subjects who prematurely discontinued. Twenty percent of this number (n=192) did so due to adverse events. Two to three times more subjects discontinued due to adverse events within the Dex treatment group vs. lansoprazole, while 25-50% less subjects discontinued due to adverse events within the Dex treatment group vs. Placebo. Most subjects in the placebo group reported dyspepsia, nausea, vomiting, esophageal ulcers and perforations as the adverse event causing discontinuation, while most subjects in the Dex treatment group reported diarrhea

and abdominal pain. Placebo discontinuation rates were statistically significant for the Maintenance of Healed EE studies, where the majority specified EE relapse as their primary reason for discontinuation.

Special adverse events of concern include cardiovascular (CV) AEs and fracture/injury-related AEs. Although there were no cardiac-related deaths, major CV AEs reported demonstrated two clinically important points: 1) ischemic coronary events, such as nonfatal MI and chest pain, only occurred in the Dex treatment groups and, 2) the incidence rate of CV AEs in the 30 mg Dex is 3-5x higher than that of placebo or lansoprazole. The rate of nonfatal MI in the 30mg Dex group (0.21/100 PM) is 10 times the expected number of (0.02/100PM) in the general US hospitalized population. This relatively high incidence rate seen in 30mg Dex was not shown in the 60mg and 90mg doses and cannot be explained by a trend or pattern. All patients with CV AEs had cardiovascular risk factors or previous medical history of cardiac events. Thus, the risk of cardiovascular adverse events is considered not significant, but concerning; such that labeling recommendations are advised.

Fracture/injury-related AEs have presented themselves in two fashions. Firstly, as an imbalance in SAEs where they were only represented in the Dex treatment groups. Secondly, upon review of both serious and nonserious AEs, the imbalance remained, with incidence rate for total Dex treatment group being almost 2x that of its comparators. Although no hip or vertebral fractures occurred in the Phase 3 studies, the majority of all other fractures occurred in the Dex treatment groups. There is no dose-related trend for injury-related AEs, however, most occurrences are fractures, falls, and joint sprains. Further postmarketing monitoring is needed to fully evaluate the risk of fractures/injury-related adverse events with Dexlansoprazole.

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 was shown 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.

There were no cases of hepatic failure, liver necrosis, liver transplant, sudden death, renal failure, agranulocytosis, aplastic anemia, bone marrow depression, pancytopenia, TT, DIC, hemolytic anemia, blind, deaf, SJS, torsades de pointes, ventricular fibrillation, or TEN.

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

Safety concerns to focus on from this discussion are cardiovascular and fracture/injury-related adverse events among the Dex treatment group versus that of lansoprazole 30mg and placebo. The incidence of such events is small, thus refuting significant reason to delay drug approval. Labeling revisions and postmarketing studies are proposed to further manage and assess these potential safety concerns.

## 7.1 Methods

Due to the combination of different doses and 3 different indications presented in the clinical plan for this application, the safety review will discuss with each section, first, all Phase 3 studies pooled together, second, the Phase 3 studies by proposed indication, then, the long-term safety study, and lastly, relevant information from the Phase 1 trials.

The sponsor's submissions 2.7.4 Summary of Clinical Safety, 5.3.5.3 Integrated Summary of Safety (ISS), 5.3.5.4 4-Month Safety Update (cutoff date 14 Jan 2008), Lansoprazole Safety Evaluation (28 Mar 2008), Response to FDA Request Dated 1 Nov 2007, Risk of Hip Fracture and Lansoprazole Use: Analysis of Post-Marketing Surveillance and Clinical Study Databases (27 Feb 2008), were adequate for the clinical safety review. Additional information was requested from the sponsor to assist in evaluation of cardiovascular and injury-related adverse events.

### 7.1.1 Clinical Studies Used to Evaluate Safety

The six well-controlled Phase 3 studies were randomized, double-blind, 3-arm, multicenter studies controlled by either placebo or active therapy (lansoprazole 30mg delayed release capsule). Two studies supported each indication. [See Table 7.1.1.1. below for brief study descriptions and Appendix Table 7.1.1.2 for more detail]

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**Table 7.1.1.1 Brief Listing of Phase 3 Safety Studies (n=7)<sup>a</sup>**

Study ID	Proposed Indication	Study Design	No. of Subjects (M/F)	Study and Control Drugs: Dose and Regimen	Treatment Duration	Status
		Control Type				Type of Report
T-EE04-084	Healing of EE	Randomized 1:1:1, double-blind parallel-group, ACTIVE	1111/927	60 mg Dex QD or 90 mg Dex QD or 30 mg lansoprazole delayed release QD	4 or 8 weeks	Completed Jan-07  Full
T-EE04-085	Healing of EE	Randomized 1:1:1, double-blind parallel-group, ACTIVE	1091/963	60 mg Dex QD or 90 mg Dex QD or 30 mg lansoprazole delayed release QD	4 or 8 weeks	Completed Jan-07  Full
T-EE04-086	Maintenance of Healed EE	Randomized 1:1:1, double-blind parallel-group, PLACEBO	235/216	60 mg Dex QD or 90 mg Dex QD or placebo QD	6 months	Completed Nov-06  Full
T-EE05-135	Maintenance of Healed EE	Randomized 1:1:1, double-blind parallel-group, PLACEBO	215/230	30 mg Dex QD or 60 mg Dex QD or placebo QD	6 months	Completed May-07  Full
T-GD04-082	Symptomatic Non-erosive GERD	Randomized 1:1:1, double-blind, multicenter, parallel-group, PLACEBO	265/643	60 mg Dex QD or 90 mg Dex QD or placebo QD	4 weeks	Completed May-06  Full
T-GD05-137	Symptomatic Non-erosive GERD	Randomized 1:1:1, double-blind, multicenter, parallel-group PLACEBO	274/673	30 mg Dex QD or 60 mg Dex QD or placebo QD	4 weeks	Completed Dec-06  Full
T-GI04-088	Long-Term Safety	Open-label, Randomized 1:1, multicenter, long-term extension	96/217 <sup>b</sup>	60 mg Dex QD or 90 mg Dex QD	12 months	Ongoing for Amendment 4  Interim (Final expected 1Q 2009)

<sup>a</sup> Derived from sponsor's Table 5.2.a., pages 13-18 of 5.2 Tabular Listings of All Clinical Studies.

<sup>b</sup> Total enrolled as of November 28, 2007, under Amendments 1 to 4.

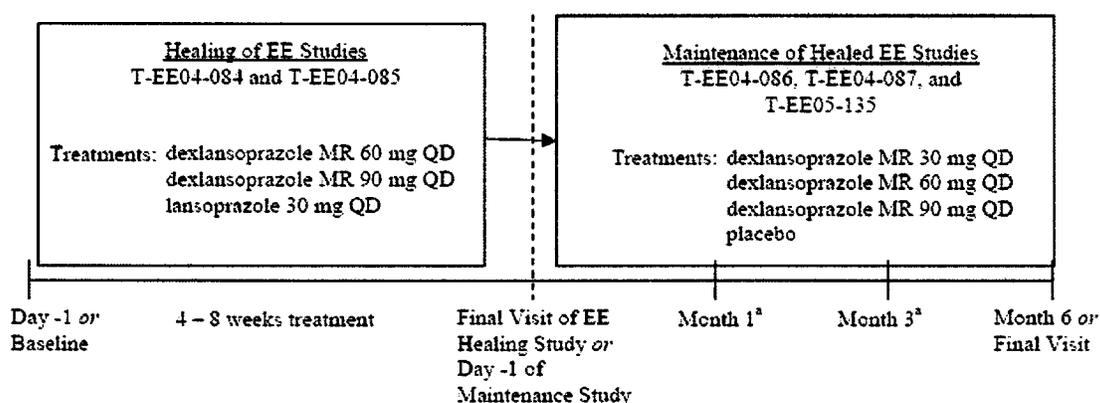
**Reviewer's Comments**

*The sponsor's amendments to the original clinical study protocols included FDA pre-submission recommendations to add a lower dose than 60mg and 90mg Dexlansoprazole. This is demonstrated with the 30mg Dex treatment group in studies T-EE05-135 and T-GD05-137. A*

*direct comparison of 30mg Dexlansoprazole and active control 30mg lansoprazole was not examined.*

Subjects completing 4 or 8 weeks of the Healing of EE (HEE) studies, with healed erosive esophagitis by endoscopic exam, were rolled into the 6-month Maintenance of Healed EE (MHEE) studies and re-randomized to the new treatment groups (with a screening period 7-21 days).

**Sponsor's Figure. Healing of EE and Maintenance of Healed EE Studies (p.30 of ISS)**



- a Subjects who had recurrence of EE at Month 1 or Month 3 were discontinued and Final Visit procedures were performed.

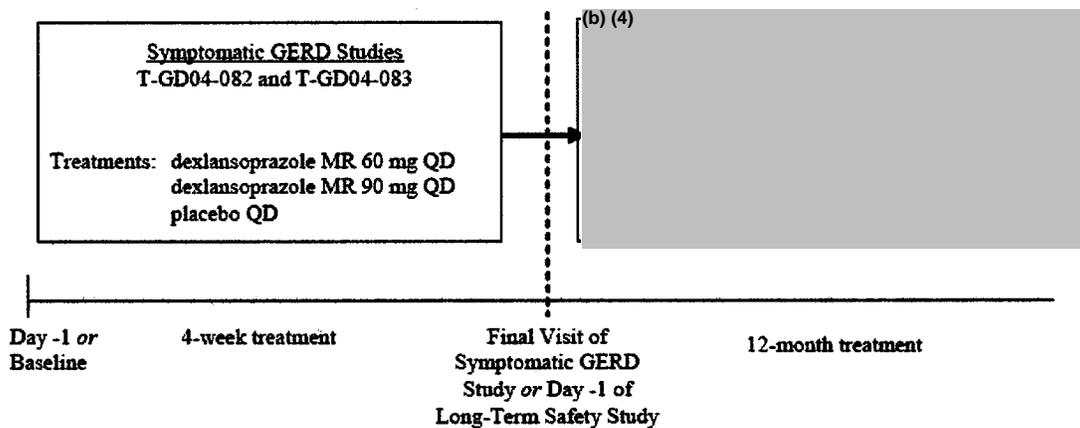
**Reviewer's Comments**

*The two HEE studies were of identical protocols, designed to prove Dexlansoprazole 60mg and 90mg non-inferior to the active control lansoprazole 30mg. There was no comparison of 30mg Dexlansoprazole and the active control. Given that, pharmacologically, Dexlansoprazole is composed only of the active ingredient of lansoprazole and formulated to provide extended therapeutic action, it may be hypothesized that Dexlansoprazole would remain non-inferior to lansoprazole in such a study and provide strong evidence for the efficacy of this new drug product.*

*The two MHEE studies were also similar studies but with different treatment groups (one with 60mg Dex/90mg Dex//Placebo, the other with 30mg Dex/60mg Dex//Placebo) designed to prove Dexlansoprazole superior to placebo. As an extension study, one patient may serve in 2 studies (HEE, MHEE) and careful monitoring is needed to ensure adverse events are associated with the concurrent study drug assignment.*

As presented in this application, subjects were rolled over from the Symptomatic GERD studies to be re-randomized into new treatment groups (with 7-21 day screening period) in the Long-Term Safety (LTS) study. The LTS was a randomized, open-label, 2-arm multicenter study. The LTS study was expanded by Amendment 4 (2007) to expose more subjects to dexlansoprazole 90mg. Amendment 4 enrolled 278 additional subjects who were diagnosed with GERD, with or without evidence of EE. Subjects did not have to complete a prior dexlansoprazole GERD study to be eligible for enrollment.

**Sponsor's Figure. Symptomatic GERD and Long-Term Safety Studies (p.31 of ISS)**



**Reviewer's Comments**

*The two GERD were similar studies but with different treatment groups (one with 60mg Dex/90mg Dex//Placebo, the other with 30mg Dex/60mg Dex//Placebo) designed to prove Dexlansoprazole superior to placebo.*

*The long-term safety study was an open-label, uncontrolled study. Again, with this extension study, one patient may serve in 2 studies (GERD, LTS).*

The Phase 1 non-clinical studies evaluated bioavailability, PK/PD, food effect, drug-drug interaction, cardiac repolarization and use in special population. Studies include 7 single-dose studies (T-P104-069, T-P104-092, T-P105-115, T-P105-119, T-P106-146, T-P106-148, T-P106-149) and 9 multiple-dose studies (T-P104-071, T-P104-100, T-P105-122, T-P105-129, T-P105-132, T-P105-133, T-P105-134, T-P105-139, T-P106-141) which used the same formulation of dexlansoprazole as that used in Phase 3 clinical trials. [See Table 7.1.1.3. in Appendix for brief descriptions of Phase 1 studies.] In single-dose studies, 283 subjects received dexlansoprazole, while 241 subjects received dexlansoprazole in multiple-dose studies. Doses ranged from 30 mg to 300 mg daily.

### 7.1.2 Adequacy of Data

All adverse events were coded using MedDRA Version 10.0 and recorded on case report forms. Adverse events were recorded if they occurred after the first dose of the study drug through 30 days after stopping the study drug. **The sponsor defines an adverse event (AE) as “any unfavorable, unintended or untoward sign, symptom or disease temporally associated with use of a medicinal product, whether or not considered related to the medicinal product”. In accordance with 21 CFR 312.32 (a), a serious adverse event (SAE) was any adverse event that resulted in “death, a life threatening adverse event experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect” or an adverse event that, based on clinical judgment, may have jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes mentioned above. Serious adverse events are reported on Council for International Organizations of Medical Sciences (CIOMS) forms.**

#### **Reviewer’s Comments**

*Appropriate coding to MedDRA class categorization was appropriate for most of the investigator/patient preferred terms. However, the preferred term of “chest pain” could have been better coded to the SOC of Cardiac Disorders instead of Pain and Discomfort NEC when the pain was found to be of cardiac origin. Additionally, preferred term “chest discomfort” would have been better coded to SOC Pain and Discomfort NEC rather than General Signs and Symptoms NEC.*

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

All Phase 3 studies were combined and summary tables were produced for adverse events, serious adverse events, adverse events leading to premature discontinuations of study drug, and adverse events of special interest. Data from all Phase 3 safety studies were pooled, as well as summarized separately in 4 study groups based on indication and/or treatment duration (i.e. long-term safety study). All Phase 1 studies were combined and summarized into 2 study groups: single-dose studies and multiple-dose studies.

Due to the different lengths of exposure determined by study designs and treatment group imbalances caused by premature discontinuations, the adverse event incidence rates for the MHEE indication grouping and all Phase 3 grouping were additionally measured by patient-month (PM). PM instead of patient-year was used in the analyses because all studies except the long-term safety study had a study duration of 6 months or less. The most frequently reported adverse events by PM of exposure were defined as those high level terms (HLTs) occurring in at least 1 subject per 100 PM of exposure in  $\geq 1$  treatment group. In HEE, GERD, and LTS groupings, AE risk was measured by proportion because the treatment groups were more balanced and had less premature discontinuations. The most frequently reported adverse events were defined as those HLTs occurring in  $\geq 5\%$  (prior to rounding) of

subjects in  $\geq 1$  treatment group. For comparison purposes across the 3 proposed indications, all adverse events were also summarized by PM of exposure for the HEE, GERD, and LTS.

Adverse events of special interest were also summarized by PM of exposure and numbers and percentages of subjects in following categories: potential cardiovascular disease, upper respiratory tract infections, lower respiratory tract infections, hepatic enzymes abnormalities, cholelithiasis and cholecystitis, gastric polyps, hip and vertebral fracture and calcium homeostasis, and anemia.

## 7.2 Adequacy of Safety Assessments

The methods used to monitor and assess safety included physical examinations, vital signs, clinical laboratory tests, fasting serum gastrin levels, electrocardiograms (ECGs), prior and concomitant medication assessment, reported adverse events, endoscopy, and gastric biopsies. ECGs were assessed in all Phase 1 studies and one Phase 3 GERD study. Phase 1 studies were used to evaluate QT/QTc prolongation. Gastric biopsies were performed for MHEE and LTS studies, with baseline biopsies occurring during HEE and GERD studies if the particular study site also hosted the MHEE and LTS Studies.

### Reviewer's Comment

*The above methods were appropriate for safety evaluation of Dexlansoprazole.*

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

#### 7.2.1.1. Overall Exposure

In the development program for Dexlansoprazole, there was adequate patient exposure per ICH guidelines to proposed drug dosages for marketing. There were 5072 patients exposed to at least one dose Dexlansoprazole with a mean exposure of  $72.7 \pm 92.01$  days. Of the 5072 subjects, 597 were exposed for at least 24 weeks, and 203 exposed for at least 48 weeks. [See Table 7.2.1.1.] Of the highest proposed dosage to be marketed (90mg), 2537 patients received at least one dose, 279 were exposed for at least 24 weeks, and 95 exposed for at least 48 weeks.

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**Table 7.2.1.1. Overall Exposure in Phase 1 & Phase 3 Clinical Studies<sup>1</sup>**

	Treatment Group							Lansoprazole 30 mg QD (N=1484)
	Placebo (N=933)	Dexlansoprazole					Total <sup>2</sup> (N=5072)	
		30 mg QD (N=511)	60 mg QD (N=2456)	90 mg QD (N=2537)	120 mg QD (N=75)	300 mg QD (N=38)		
<b>Duration (Weeks)</b>								
0-<4	285	137	522	700	75	38	1204	308
4-<8	584	265	1194	1007	0	0	2182	788
8-<12	4	2	351	334	0	0	679	386
12-<24	21	15	60	67	0	0	144	2
24-<36	39	92	215	279	0	0	597	0
36-<48	0	0	8	55	0	0	63	0
≥48	0	0	106	95	0	0	203	0
<b>Summary Statistics (Days)</b>								
Mean ± SD	34.2 ± 33.63	55.4 ± 61.09	64.6 ± 83.27	71.4 ± 92.68	5.0 ± 0.00	1.0 ± 0.00	72.7 ± 92.01	36.8 ± 17.51
Median	28.0	29.0	31.0	31.0	5.0	1.0	31.0	32.0
Min-Max	1-198	1-201	1-454	1-421	5-5	1-1	1-454	1-97
<b>Cumulative Exposure</b>								
≥1 day	933	511	2456	2537	75	38	5072	1484
≥4 weeks	648	374	1934	1837	0	0	3868	1176
≥8 weeks	64	109	740	830	0	0	1686	388
≥12 weeks	60	107	389	496	0	0	1007	2
≥24 weeks	39	92	329	429	0	0	863	0
≥36 weeks	0	0	114	150	0	0	266	0
≥48 weeks	0	0	106	95	0	0	203	0

<sup>1</sup> Sponsor's Table 2. of 5.3.5.3. 4-Month Safety Update, p. 25.

<sup>2</sup> Note: Subjects who received study drug from more than 1 treatment group are counted in each of the treatment groups. The "Total" column displays exposure regardless of treatment and is not necessarily the sum of the numbers in the individual treatment columns.

In Phase 3 studies, 1363 subjects received the active control lansoprazole and 896 subjects received placebo.

In the HEE and GERD studies, mean exposure to study drug was similar in the Dexlansoprazole and control groups. However, because of the high premature discontinuation rates among the placebo group in the MHEE studies due to relapse of EE, mean exposure to study drug was >2x higher for the Dexlansoprazole groups. See table below.

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**Table 7.2.1.2. Mean Exposure by Indication and Treatment Group in Phase 3 Studies<sup>1</sup>**

Study Indication	Treatment Group					
	Placebo (N=933)	Dexlansoprazole				Lansoprazole 30 mg QD (N=1484)
		30 mg QD (N=511)	60 mg QD (N=2456)	90 mg QD (N=2259)	Total (N=4794)	
<b>Mean ± SD</b>						
<b>HEE</b>	--	--	38.2 ± 15.22	38.1 ± 14.90	38.1 ± 15.06	39.6 ± 15.35
<b>MHEE</b>	52.9 ± 54.92	136.6 ± 65.52	140.3 ± 60.84	134.9 ± 63.57	138.1 ± 62.57	--
<b>GERD</b>	27.4 ± 5.95	28.1 ± 5.53	27.8 ± 6.20	27.2 ± 6.34	27.8 ± 6.08	--
<b>LTS</b>	--	--	285.8 ± 131.14	267.1 ± 137.76	276.2 ± 134.67	--

<sup>1</sup> Reviewer's Table; adapted from Sponsor's Tables 12, 13, 14, 15 of 5.3.5.3 Integrated Summary of Safety, p. 74-6.

**7.2.1.2. Demographics**

In all Phase 3 trials, there were no differences in baseline demographic characteristics by treatment groups, except for gender. Subjects were mostly White (84-87%), Non-Hispanic (81-92%), Non/Ex-Smokers (75-81%), and Caffeine Users (78-83%) with mean age of approximately 48 years and mean BMI of approximately 30 kg/m<sup>2</sup>. [See Table 7.2.1.3.] More women than men (2:1) were demonstrated in the placebo and dexlansoprazole 30mg groups. The sponsor reasons that this difference occurs because these treatment groups were not used in Healing of EE trials and more women were enrolled in the Symptomatic GERD trials. In addition, many of the subjects in the GERD trials were rolled over into the LTS study. The majority of all subjects enrolled in the LTS prior to Amendment 4 were female (69%), white (81%), and under 65 years of age (88%). In general, for any baseline demographic characteristics, there was no statistically significant difference between treatment groups, and no interaction when analyzed by study indication.

**Table 7.2.1.3. Demographics and Baseline Characteristics in All Phase 3 Studies<sup>1</sup>**

Variable	Treatment Group					
	Placebo (N=896)	Dexlansoprazole				Lansoprazole 30 mg (N=1363)
		30 mg (N=455)	60 mg (N=2311)	90 mg (N=2142)	Total (N=4548)	
<b>Gender: n (%)</b>						
Male	302 (34)	153 (34)	1094 (47)	1003 (47)	2078 (46)	727 (53)
Female	594 (66)	302 (66)	1217 (53)	1139 (53)	2470 (54)	636 (47)
<b>Ethnicity: n (%)</b>						
Hispanic or Latino	157 (18)	88 (19)	281 (12)	247 (12)	561 (12)	112 (8)
Not Hispanic or Latino	739 (82)	367 (81)	2030 (88)	1895 (88)	3987 (88)	1251 (92)
<b>Race: n (%)</b>						

Variable	Treatment Group					
	Placebo (N=896)	Dexlansoprazole				Lansoprazole 30 mg (N=1363)
		30 mg (N=455)	60 mg (N=2311)	90 mg (N=2142)	Total (N=4548)	
American Indian/Alaska Native	8 (<1)	0	23 (<1)	30 (1)	49 (1)	14 (1)
Black of African Heritage	94 (10)	43 (9)	191 (8)	151 (7)	348 (8)	59 (4)
Native Hawaiian or Other Pacific Islander	4 (<1)	1 (<1)	6 (<1)	1 (<1)	7 (<1)	1 (<1)
Asian	19 (2)	7 (2)	89 (4)	84 (4)	170 (4)	58 (4)
White	757 (84)	394 (87)	1958 (85)	1823 (85)	3872 (85)	1186 (87)
Multiracial	11 (1)	7 (2)	40 (2)	50 (2)	92 (2)	41 (3)
Missing Data	3 (<1)	3 (<1)	4 (<1)	3 (<1)	10 (<1)	4 (<1)
Age (yr) <sup>a</sup>						
<45: n (%)	336 (38)	185 (41)	913 (40)	876 (41)	1844 (41)	582 (43)
45-<65: n (%)	457 (51)	225 (49)	1145 (50)	1041 (49)	2216 (49)	646 (47)
≥65: n (%)	103 (11)	45 (10)	253 (11)	225 (11)	488 (11)	135 (10)
N	896	455	2311	2142	4548	1363
Mean ± SD	48.4±13.67	47.4±13.41	48.1±13.51	47.7±13.76	47.8±13.63	47.3±13.69
Median	49.0	49.0	48.0	48.0	48.0	47.0
Min-Max	18-86	18-85	18-85	18-90	18-90	18-87
Weight (kg) <sup>a</sup>						
N	896	455	2306	2140	4542	1363
Mean ± SD	83.2±19.85	83.4±20.07	85.9±19.70	85.5±19.29	85.4±19.61	86.8±18.87
Median	80.7	81.7	84.1	84.0	83.5	85.4
Min-Max	41-166	42-165	37-193	38-185	37-193	43-165
Height (cm) <sup>a</sup>						
N	894	454	2293	2119	4508	1354
Mean ± SD	167.3±9.94	167.7±9.70	169.4±10.28	169.2±10.39	169.2±10.24	170.4±10.35
Median	165.4	167.6	168.9	168.0	168.0	170.2
Min-Max	128-194	133-193	124-213	135-198	124-213	122-198
BMI (kg/m <sup>2</sup> ) <sup>a</sup>						
<25: n (%)	227 (25)	113 (25)	494 (21)	433 (20)	973 (21)	251 (18)
25-<30: n (%)	293 (33)	157 (35)	827 (36)	794 (37)	1651 (36)	534 (39)
≥30: n (%)	374 (42)	184 (40)	968 (42)	891 (42)	1880 (41)	569 (42)
Missing Data: n (%)	2 (<1)	1 (<1)	22 (<1)	24 (1)	44 (<1)	9 (<1)
N	894	454	2289	2118	4504	1354
Mean ± SD	29.7±6.68	29.6±6.79	30.0±6.62	29.8±6.22	29.8±6.48	29.9±6.15
Median	28.6	28.7	28.8	29.0	28.9	28.9
Min-Max	17-59	17-68	15-81	14-75	14-81	16-81
Alcohol Use: n (%)						
Drinker	487 (54)	228 (50)	1319 (57)	1214 (57)	2558 (56)	752 (55)
Non-/Ex-Drinker	409 (46)	227 (50)	992 (43)	928 (43)	1990 (44)	608 (45)
Smoking Status: n (%)						
Smoker	172 (19)	109 (24)	514 (22)	504 (24)	1036 (23)	340 (25)
Non-/Ex-Smoker	724 (81)	346 (76)	1797 (78)	1638 (76)	3512 (77)	1022 (75)
Caffeine Use: n (%)						
Caffeine Use	703 (78)	379 (83)	1818 (79)	1721 (80)	3621 (80)	1085 (80)
Non-Caffeine Use	193 (22)	76 (17)	493 (21)	420 (20)	926 (20)	276 (20)

<sup>1</sup> Sponsor's Table 7. of 5.3.5. 4-Month Safety Update, pp. 34-35.

<sup>a</sup> At baseline.

In all Phase 1 studies, there were no differences in baseline demographic characteristics by single-dose or multiple-dose groupings. Subjects were mostly Male (66%), White (68%), Non-Hispanic (64%) with mean age of approximately 34.8 years and mean BMI of 26.0 kg/m<sup>2</sup> (data not shown).

#### **Reviewer's Comments**

*The safety population differs from efficacy population by inclusion of the LTS population and the Phase I study population. Additionally, the safety population, from the MHEE and LTS studies, is composed of those who proved to be responders in either the HEE or GERD studies. Response itself is multifactorial but may indicate better patient compliance with the drug regimen or the presence of less severe disease.*

*The disproportion of enrollment by gender in the GERD studies does not lie in agreement with the background epidemiology of GERD, where GERD affects men and women in nearly equal proportions (Fass 2007). Fortunately, this disproportion was shown not to modify the results of the GERD studies, nor the following LTS study.*

#### 7.2.2 Explorations for Dose Response

Through Phase 1 studies, the pharmacodynamics of dexlansoprazole was assessed to measure increases in intragastric pH. Dose-response analyses indicated that Dex (at doses 30 to 90 mg) caused an increase in gastric pH similar or higher than lansoprazole. The sponsor explains that doses of dexlansoprazole 30 mg or lower would be unlikely to provide gastric acid suppression greater than lansoprazole, while doses higher than 90 mg would be unlikely to provide meaningful additional pharmacological benefit. Doses 60 and 90 mg were selected for the Phase 3 healing of EE studies, while lower doses 30mg and 60mg were used in MHEE and GERD studies.

#### 7.2.3. Special Animal and/or In Vitro Testing

Animal testing relevant to human safety found Dexlansoprazole similar to lansoprazole. A more comprehensive review of preclinical data associated with this application is found in the Pharmacology/Toxicology review by Dr. K. Zhang.

#### 7.2.4. Routine Clinical Testing

Routine clinical testing was performed at specified visits outlined in the Phase 3 study protocols. These routine laboratory evaluations included those listed in the table below, as well as serum pregnancy tests in all females.

**Table 3. Routine Laboratory Evaluations in the Phase 3 Studies**

Hematology	Urinalysis
Hemoglobin	Specific gravity
Hematocrit	pH
Red blood cell (RBC) count	Glucose
Red cell indices	Ketones
Platelet count	Microscopic examination
White blood cell (WBC) count with differential	Protein
Serum Chemistry	
Albumin	Glucose
Alkaline phosphatase	Inorganic phosphorus
Alanine aminotransferase (ALT)	Potassium
Aspartate aminotransferase (AST)	Sodium
Blood urea nitrogen (BUN)	Total bilirubin
Calcium	Total cholesterol
Chloride	Total protein
Creatinine	Uric acid

From the Sponsor's Integrated Summary of Safety, 5.3.5.3, p.41.

**Reviewer's Comments:**

*These routine clinical testing methods were appropriate to monitor for adverse event information.*

**7.2.5. Metabolic, Clearance, and Interaction Workup**

Dexlansoprazole's metabolism, clearance, and interaction with other concomitantly administered drugs were properly evaluated and are best discussed in the Clinical Pharmacology review by Dr. J.P. Bai.

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

The sponsor performed adequate analyses to evaluate potential adverse events known to the drug class, suggested by sporadic results of Dexlansoprazole trials, and of the current public safety concern. Analyses of special adverse events are presented in section 7.3.4. of the present document.

**7.3 Major Safety Results**

**7.3.1 Deaths**

There were seven (7) total deaths occurring in the dexlansoprazole development program. All deaths occurred in the Phase 3 studies; no deaths were reported in Phase 1 trials. Of the 7 deaths, 5 occurred in patients taking dexlansoprazole 60mg, 1 occurred in a patient taking dexlansoprazole 90mg, and 1 occurred in a patient taking lansoprazole 30mg. No deaths are reported in the placebo treatment group. Six of the seven subjects had discontinued treatment

before the end of the study period. Two of the seven deaths were due to malignancy, two related to surgical procedures, two due to chronic disease, and one non-study drug overdose.

**Table 7.3.1.1. Brief Description of Deaths in Dexlansoprazole Development Program**

<u>DEXLANSOPRAZOLE 60 MG QD</u>		
• TGD04082-11382007#	45M	Acute Methadone Toxicity
• TEE04084-32457009#	48M	End Stage Liver Disease, Hepatic Coma & Malnutrition
• TEE04085-11333014#	50F	Stomach Cancer
• TGI04088-32128005#	78F	Severe Respiratory Failure Secondary To Acute Promyelocytic Leukemia
• TGI04088-9223002#	45F	Acute Respiratory Failure
<u>DEXLANSOPRAZOLE 90 MG QD</u>		
• TGI04088-9172013#	64F	Sepsis D/T Fracture Of Right Elbow, Repaired
<u>LANSOPRAZOLE 30 MG QD</u>		
• TEE04084-32460061	58F	Liposuction Surgery

(# prematurely discontinued study drug)

During the Screening Period, prior to study drug administration, one patient, with a history of depression and drug abuse, died due to methadone intoxication and cocaine use. For further description of deaths, see Appendix for Table 7.3.1.2. Phase 3 Clinical Studies Deaths Listing.

The table below demonstrates a similar mortality rate between dexlansoprazole and lansoprazole; however, among the dexlansoprazole treatment group, the majority of deaths occurred in the 60mg QD group.

**Table 7.3.1.2.<sup>1</sup> Overall Summary of Deaths by 100 PM of Exposure in All Phase 3 Studies**

	Treatment Group: n (rate per 100 PM)					
	Placebo (N=896)	Dexlansoprazole				Lansoprazole
		30 mg QD (N=455)	60 mg QD (N=2311)	90 mg QD (N=2142)	Total (N=4548)	30 mg QD (N=1363)
Average Patient-Months of Exposure	1.2	2.1	2.3	2.8	2.7	1.3
Deaths	0	0	5 (0.09)	1 (0.02)	6 (0.05)	1 (0.06)

<sup>1</sup> Sponsor's Table 12. Overall Summary of Deaths by 100 PM of Exposure in All Phase 3 Studies, 5.3.5.3 4-Month Safety Update, p.53.

**Reviewer's Comments**

*As the study investigators considered all deaths not related to the study drug, the value of demonstrating five deaths on dexlansoprazole 60mg is uncertain. This reviewer finds no common associations among the deaths that convincingly implicate Dexlansoprazole as a primary cause. Two deaths were unanticipated, the methadone toxicity and surgical complication post liposuction, while the other 5 resulted from chronic diseases or ongoing processes.*

### 7.3.2 Nonfatal Serious Adverse Events

Sixty-eight subjects, of the 6,807 participating in the Phase 3 clinical trials, reported  $\geq 1$  treatment-emergent nonfatal serious adverse events (SAE). Overall SAE 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.

**Table 7.3.2.1. Nonfatal Serious Adverse Events in All Phase 3 Studies**

Total Subjects With $\geq 1$ Adverse Event	Treatment Group: n (rate per 100 PM)							Lansoprazole 30 mg QD (N=1363) (Avg PM=1.3)
	Placebo (N=896) (Avg PM=1.2)	Dexlansoprazole					Updated <sup>a</sup> Total (N=4548) (Avg PM=2.7)	
		30 mg (N=455) (Avg PM=2.1)	60 mg (N=2311) (Avg PM=2.3)	90 mg (N=1864) (Avg PM=2.2)	Updated <sup>a</sup> 90 mg (N=2142) (Avg PM=2.8)	Total 90mg (N=4270) (Avg PM=2.4)		
n (%)	2 (0.2)	4 (0.9)	26 (1.1)	22 (1.2)	29 (1.4)	52 (1.2)	59 (1.3)	7 (0.5)
Rate per 100PM	0.19	0.43	0.49	0.54	0.49	0.50	0.48	0.39
<i>Rate Ratio compared to Placebo</i>		<i>2.6 (0.8-15.7)</i>						
<i>Rate Ratio compared to Lansoprazole</i>		<i>1.2 (0.6-2.9)</i>						

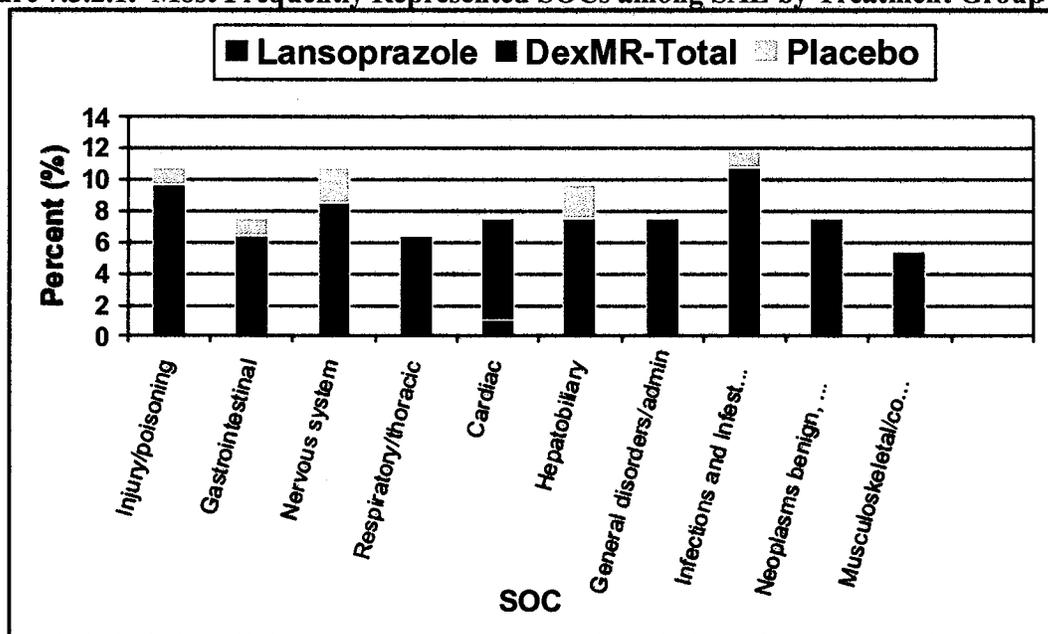
-Reviewer's Table. Adapted from Sponsor's Table 18. Treatment-Emergent Nonfatal Serious Adverse Events per 100 PM of Exposure in All Phase 3 Studies, 5.3.5.4. 4-Months Safety Update, pp. 61-69.

Although no single SAE occurred at a rate  $>0.3$  cases per 100PM per treatment group, the total Dex treatment population demonstrated 1.2-2.5 x higher non-fatal SAE incidence rates than lansoprazole 30mg or placebo.

Examining the proportion of SAE by treatment group also showed the highest risk among the Dex treatment groups. The Dex had approximately 3 to 6 times higher SAE 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. By either method, there appears to be a dose-related trend where more SAEs occur with increasing dose of Dexlansoprazole. Further evaluation shows that among all SAEs, most occurred in the system organ classes (SOC) of infections, injury, and nervous system disorders.

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Figure 7.3.2.1. Most Frequently Represented SOC among SAE by Treatment Group\*



\*Reviewer's Figure.

When isolated, the SAE SOC of Infections/Infestations does have the most number of events occurring in the Dexlansoprazole treatment groups. However, comparison of the Dexlansoprazole treatment groups' incidence rates with that of lansoprazole finds the two study drugs comparable. See table below.

Table 7.3.2.2. Infection Nonfatal Serious Adverse Events in All Phase 3 Studies

INFECTION SAEs  MedDRA High Level Term Preferred Term	Treatment Group: n (rate per 100 PM)					
	Placebo (N=896) (Avg. PM=1.2)	Dexlansoprazole				Lansoprazole 30 mg QD (N=1363) (Avg. PM=1.3)
		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)	
Total Subjects With ≥1 Adverse Event	2 (0.19)	4 (0.43)	26 (0.49)	29 (0.48)	59 (0.48)	7 (0.39)
<b>Cholecystitis and Cholelithiasis</b>	0	0	2 (0.04)	3 (0.05)	5 (0.04)	2 (0.11)
Cholecystitis	0	0	1 (0.02)	2 (0.03)	3 (0.02)	1 (0.06)
Cholecystitis Chronic	0	0	0	1 (0.02)	1 (<0.01)	0
Cholelithiasis	0	0	2 (0.04)	0	2 (0.02)	1 (0.06)
<b>Sepsis, Bacteremia, Viraemia and Fungaemia NEC</b>	0	1 (0.11)	1 (0.02)	0	2 (0.02)	0
Sepsis	0	1 (0.11)	1 (0.02)	0	2 (0.02)	0
<b>Streptococcal Infections</b>	0	0	0	0	0	1 (0.06)
Pneumonia Streptococcal	0	0	0	0	0	1 (0.06)
<b>Abdominal and Gastrointestinal Infections</b>	0	0	2 (0.04)	1 (0.02)	3 (0.02)	0
Diverticulitis	0	0	1 (0.02)	0	1 (<0.01)	0
Gastroenteritis	0	0	1 (0.02)	1 (0.02)	2 (0.02)	0

<i>INFECTION SAEs</i>	Treatment Group: n (rate per 100 PM)					
	Placebo (N=896) (Avg. PM=1.2)	Dexlansoprazole			Total (N=4548) (Avg. PM=2.7)	Lansoprazole 30 mg QD (N=1363) (Avg. PM=1.3)
		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)		
MedDRA High Level Term Preferred Term						
<b>Lower Respiratory Tract and Lung Infections</b>	0	0	2 (0.04)	0	2 (0.02)	0
Pneumonia	0	0	2 (0.04)	0	2 (0.02)	0
<b>Acute and Chronic Pancreatitis</b>	0	0	0	1 (0.02)	1 (<0.01)	0
Pancreatitis	0	0	0	1 (0.02)	1 (<0.01)	0
<b>Urinary Tract Infections</b>	0	0	0	1 (0.02)	1 (<0.01)	0
Urinary Tract Infection	0	0	0	1 (0.02)	1 (<0.01)	0
<b>Bacterial Infections NEC</b>	0	0	1 (0.02)	0	1 (<0.01)	0
Cellulitis	0	0	1 (0.02)	0	1 (<0.01)	0
<b>Implant and Catheter Site Reactions</b>	0	0	1 (0.02)	0	1 (<0.01)	0
Catheter Related Complication	0	0	1 (0.02)	0	1 (<0.01)	0
<b>Infections NEC</b>	0	0	1 (0.02)	0	1 (<0.01)	0
Postoperative Wound Infection	0	0	1 (0.02)	0	1 (<0.01)	0
<b>Peritoneal and Retroperitoneal Disorders</b>	0	0	1 (0.02)	0	1 (<0.01)	0
Peritonitis	0	0	1 (0.02)	0	1 (<0.01)	0
<b>Upper Respiratory Tract Infections</b>	0	0	1 (0.02)	0	1 (<0.01)	0
Sinusitis	0	0	1 (0.02)	0	1 (<0.01)	0
<b>Viral Infections NEC</b>	0	0	1 (0.02)	0	1 (<0.01)	0
Gastroenteritis Viral	0	0	1 (0.02)	0	1 (<0.01)	0
<b>All SAE Infections/Infestations</b>	0	1 (0.11)	13 (0.24)	6 (0.10)	20 (0.16)	3 (0.17)

Adapted from Sponsor's Table 18. Treatment-Emergent Nonfatal Serious Adverse Events per 100 PM of Exposure in All Phase 3 Studies, 5.3.5.4. 4-Months Safety Update, pp. 61-69.

When isolated, the SAE SOC of Injury only has events occurring in the Dexlansoprazole treatment groups. The incidence rates display a dose-related trend where incidence (0, 0.11, and 0.25 subjects per 100PM) increases with increasing dose (30mg, 60mg, and 90mg Dexlansoprazole, respectively). [See Table 7.3.2.3. below.] 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.

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**Table 7.3.2.3. Injury-Related Nonfatal Serious Adverse Events in All Phase 3 Studies**

<i>INJURY-RELATED SAEs</i>	Treatment Group: n (rate per 100 PM)					
	Placebo (N=896) (Avg. PM=1.2)	Dexlansoprazole				Lansoprazole 30 mg QD (N=1363) (Avg. PM=1.3)
		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)	
MedDRA High Level Term Preferred Term						
Total Subjects With ≥1 Adverse Event	2 (0.19)	4 (0.43)	26 (0.49)	29 (0.48)	59 (0.48)	7 (0.39)
<b>Non-Site Specific Injuries NEC</b>	<b>0</b>	<b>0</b>	<b>3 (0.06)</b>	<b>5 (0.08)</b>	<b>8 (0.07)</b>	<b>0</b>
Arthropod Bite	0	0	0	1 (0.01)	1 (<0.01)	0
Fall	0	0	1 (0.02)	4 (0.06)	5 (0.04)	0
Foreign Body Trauma	0	0	1 (0.02)	0	1 (<0.01)	0
Injury	0	0	1 (0.02)	0	1 (<0.01)	0
<b>Disturbances In Consciousness NEC</b>	<b>0</b>	<b>0</b>	<b>1 (0.02)</b>	<b>1 (0.01)</b>	<b>2 (0.02)</b>	<b>0</b>
Syncope	0	0	1 (0.02)	1 (0.01)	2 (0.02)	0
<b>Inner Ear Signs and Symptoms</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.01)</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Vertigo Positional	0	0	0	1 (0.01)	1 (<0.01)	0
<b>Lower Limb Fractures and Dislocations</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.01)</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Ankle Fracture	0	0	0	1 (0.01)	1 (<0.01)	0
<b>Musculoskeletal and Connective Tissue Signs and Symptoms NEC</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.01)</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Musculoskeletal Discomfort	0	0	0	1 (0.01)	1 (<0.01)	0
<b>Perception Disturbances</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.01)</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Hallucination, Auditory	0	0	0	1 (0.01)	1 (<0.01)	0
<b>Thoracic Cage Fractures and Dislocations</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.01)</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Rib Fracture	0	0	0	1 (0.01)	1 (<0.01)	0
<b>Upper Limb Fractures and Dislocations</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.01)</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Upper Limb Fracture	0	0	0	1 (0.01)	1 (<0.01)	0
<b>Limb Injuries NEC (Incl Traumatic Amputation)</b>	<b>0</b>	<b>0</b>	<b>1 (0.02)</b>	<b>0</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Limb Injury	0	0	1 (0.02)	0	1 (<0.01)	0
<b>Site Specific Injuries NEC</b>	<b>0</b>	<b>0</b>	<b>1 (0.02)</b>	<b>0</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Back Injury	0	0	1 (0.02)	0	1 (<0.01)	0
<b>Intervertebral Disc Disorders NEC</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>2 (0.03)</b>	<b>2 (0.02)</b>	<b>0</b>
Intervertebral Disc Protrusion	0	0	0	2 (0.03)	2 (0.02)	0
<b>Joint Related Disorders NEC</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.01)</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Joint Instability	0	0	0	1 (0.01)	1 (<0.01)	0
<b>All SAE Injury-related</b>	<b>0</b>	<b>0</b>	<b>6 (0.11)</b>	<b>15 (0.25)</b>	<b>21 (0.17)</b>	<b>0</b>

Adapted from Sponsor's Table 18. Treatment-Emergent Nonfatal Serious Adverse Events per 100 PM of Exposure in All Phase 3 Studies, 5.3.5.4. 4-Months Safety Update, pp. 61-69.

When isolated, the SAE SOC of Nervous System Disorders has events occurring in both the Dexlansoprazole and lansoprazole treatment groups. The incidence rates among Dexlansoprazole display a reverse dose-related trend where incidence (0.22, 0.11, and 0.05 subjects per 100PM) decreases with increasing dose (30mg, 60mg, and 90mg Dexlansoprazole, respectively). However, comparison of the Dexlansoprazole treatment groups' incidence rates with that of lansoprazole finds the two study drugs relatively comparable. See the table below.

**Table 7.3.2.4. Nervous System Nonfatal Serious Adverse Events in All Phase 3 Studies**

MedDRA High Level Term	Treatment Group: n (%)					
	Placebo (N=896)	Dexlansoprazole				Lansoprazole 30 mg QD (N=1363)
		30 mg QD (N=455)	60 mg QD (N=2311)	90 mg QD (N=2142)	Total (N=4548)	
<b>Total Subjects With ≥1 Adverse Event</b>	<b>2 (0.22)</b>	<b>4 (0.88)</b>	<b>26 (1.13)</b>	<b>22 (1.35)</b>	<b>52 (1.30)</b>	<b>7 (0.51)</b>
<b>Central Nervous System Hemorrhages and Cerebrovascular Accidents</b>	<b>0</b>	<b>1 (0.22)</b>	<b>0</b>	<b>0</b>	<b>1 (0.02)</b>	<b>1 (0.07)</b>
Cerebrovascular Accident	0	1 (0.22)	0	0	1 (0.02)	1 (0.07)
<b>Facial Cranial Nerve Disorders</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.07)</b>
Facial Palsy	0	0	0	0	0	1 (0.07)
<b>Paralysis and Paresis (Excl Cranial Nerve)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.07)</b>
Hemiparesis	0	0	0	0	0	1 (0.07)
<b>Migraine Headaches</b>	<b>0</b>	<b>0</b>	<b>2 (0.09)</b>	<b>0</b>	<b>2 (0.04)</b>	<b>0</b>
Migraine	0	0	2 (0.09)	0	2 (0.04)	0
<b>Disturbances In Consciousness NEC</b>	<b>0</b>	<b>0</b>	<b>1 (0.04)</b>	<b>1 (0.05)</b>	<b>2 (0.04)</b>	<b>0</b>
Syncope	0	0	1 (0.04)	1 (0.05)	2 (0.04)	0
<b>Acute Polyneuropathies</b>	<b>0</b>	<b>0</b>	<b>1 (0.04)</b>	<b>0</b>	<b>1 (0.02)</b>	<b>0</b>
Guillain-Barre Syndrome	0	0	1 (0.04)	0	1 (0.02)	0
<b>Cerebrovascular Venous and Sinus Thrombosis</b>	<b>0</b>	<b>0</b>	<b>1 (0.04)</b>	<b>0</b>	<b>1 (0.02)</b>	<b>0</b>
Central Venous Thrombosis	0	0	1 (0.04)	0	1 (0.02)	0
<b>Transient Cerebrovascular Events</b>	<b>0</b>	<b>0</b>	<b>1 (0.04)</b>	<b>0</b>	<b>1 (0.02)</b>	<b>0</b>
Transient Ischemic Attack	0	0	1 (0.04)	0	1 (0.02)	0
<b>All SAE Nervous System</b>	<b>0</b>	<b>1 (0.22)</b>	<b>6 (0.11)</b>	<b>1 (0.05)</b>	<b>8 (0.07)</b>	<b>3 (0.16)</b>

Adapted from Sponsor's Table 18. Treatment-Emergent Nonfatal Serious Adverse Events per 100 PM of Exposure in All Phase 3 Studies, 5.3.5.4. 4-Months Safety Update, pp. 61-69.

Eleven of the 68 SAEs were considered possibly related to the study drug by the study investigator. One event occurred on 60mg Dex, 8 events on 90mg Dex, and 2 events on 30mg lansoprazole. These events included non-cardiac chest pain, coronary arteriospasm, chest pain, hemiparesis, facial palsy, auditory hallucination, cholelithiasis, cholecystitis, neutropenia, B-cell lymphoma, and anaphylactic reaction. [See Table 7.3.2.5. in Appendix for detailed listing]

In Phase 3 HEE studies, 0.4% to 0.7% of subjects experienced ≥1 SAE. There were no statistically significant differences between treatment groups. Non-Cardiac Chest Pain (2 Dex 60-mg subjects [2954012 and 12800003]) and Cholecystitis (1 Dex 90-mg subject [32468002], 1 lansoprazole 30-mg subject [32470006]) were the only SAEs that occurred in >1 subject. [See Table 7.3.2.6. in the Appendix for Brief Descriptions of SAEs.]

In Phase 3 MHEE studies, 0.31 to 0.73 subjects per 100PM (0.01-0.03% subjects) among Dex treatment groups and 0.20/100PM (0.003% subjects) among placebo experienced ≥1 SAE. There were no statistically significant differences between treatment groups. Non-Cardiac Chest Pain (2 Dex 60-mg subjects [14763134 and 13239048]), Endometriosis (2 Dex 60-mg subjects [12455031 and 18128010]), and Abortion Spontaneous (1 placebo subject [9172167], 1 Dex 30-

mg subject [9172128]) were the only SAEs that occurred in >1 subject. [See Table 7.3.2.7. in the Appendix for Brief Descriptions of SAEs.]

In Phase 3 GERD studies, 0.2% to 0.6% of subjects experienced  $\geq 1$  treatment-emergent, nonfatal, serious adverse event. There were no statistically significant differences between treatment groups. Myocardial infarction was the only SAE that occurred in >1 subject (2 Dex 30-mg subjects [32454009 and 9319002]). Although both subjects had significant cardiovascular history, only subject 32454009 prematurely discontinued due to this event. [See Table 7.3.2.8. in the Appendix for Brief Descriptions of SAEs.]

For the LTS study safety reports completed through January 2008, 4.6% of subjects on the Dex 60-mg and 3.9% subjects on Dex 90-mg experienced SAEs. There were no statistically significant differences between treatment groups. Fall (4 Dex 90-mg subjects [12800007, 21457011, 32128009, 9172013]), syncope (1 Dex 60-mg subject [22438008] and 1 Dex 90-mg subject [32420010]), cholelithiasis (1 Dex 60mg [20986004] and 1 Dex 90mg [11376005]), and intervertebral disc protrusion (2 Dex 90mg subjects [31023301 and 11371304]) were the SAEs that occurred in >1 subject. The sponsor explains that no associated central nervous system adverse events (e.g., Dizziness) were associated with the reports of Fall. [See Table 7.3.2.9. in the Appendix for Brief Descriptions of SAEs.]

In Phase 1 studies, 1 SAE of Perforated Appendicitis occurred in subject (#105) on multiple-dose dexlansoprazole treatment. The investigator considered the event unrelated to the study drug.

#### Reviewer's Comments

*Similar SAE incidence rates were seen for the pair dexlansoprazole 30mg and lansoprazole 30mg, as well as the dexlansoprazole 60mg and 90mg pair. The sponsor does not comment on whether there is a statistically significant difference between these pairs' and the placebo SAE rates.*

*With the LTS study administering the highest dose of Dex for the longest period of time and having several subjects with injury-related SAEs, makes this reviewer concerned about this association. Injury-related AEs will be further discussed in Section 7.3.4.2.*

### 7.3.3 Dropouts and/or Discontinuations

During the dexlansoprazole Phase 3 program, the incidence rates of treatment-emergent adverse events leading to premature discontinuation of the study drug was 0.96-1.46/100PM among the dexlansoprazole treatment groups, 0.89/100PM for lansoprazole 30-mg and 3.48/100PM in placebo. The overall proportion of subjects who prematurely discontinued treatment was 6-33%. [See Table 7.3.3.1] The placebo treatment group shows the overall highest discontinuation. This primarily reflects the placebo study population of the MHEE trials, who discontinued treatment due to relapse of EE. Note that the majority of the placebo treatment group's primary reason for discontinuation due to EE relapse was categorized under "Other", instead of "Adverse Event".

**Table 7.3.3.1. Primary Reasons for Premature Discontinuation of Subjects in All Phase 3 Studies<sup>1</sup>**

Primary Reason for Premature Discontinuation	Placebo (N=896)	Dex 30mg (N=455)	Dex 60mg (N=2311)	Dex 90mg (N=2142)	Dex Total (N=4548)	Lansoprazole 30mg (N=1363)
Number of Subjects Prematurely Discontinued	300 (33%)	69 (15%)	310 (13%)	301 (14%)	680 (15%)	76 (6%)
Adverse Event	37 (4%)	9 (2%)	77 (3%)	68 (3%)	154 (3%)	16 (1%)
Protocol Violation	0	1 (<1%)	7 (<1%)	2 (<1%)	10 (<1%)	3 (<1%)
Lost to Follow-up	15 (2%)	9 (2%)	40 (2%)	47 (2%)	96 (2%)	16 (1%)
Withdrew Consent	58 (6%)	18 (4%)	88 (4%)	79 (4%)	185 (4%)	25 (2%)
Did not meet inclusion/exclusion criteria	4 (<1%)	1 (<1%)	28 (1%)	15 (<1%)	44 (<1%)	10 (<1%)
Other	186 (21%)	31 (7%)	70 (3%)	69 (3%)	170 (4%)	6 (<1%)

<sup>1</sup> Derived from sponsor's statistical table 2.2.2.1 Primary Reasons for Which Subjects Prematurely Discontinued Study Drug in Phase 3 Studies from 5.3.5.3 4-Month Safety Update 2008 pp. 311-313.

When premature discontinuations are specified by study indication, 7-9% in GERD trials, 6-8% in HEE trials, 32-85% in MHEE trials, and 33-39% in LTS study prematurely discontinued treatment. Discontinuation was higher in studies lasting 6 months and 12 months, the MHEE and LTS studies, respectively. Again, the higher discontinuation rate of 85% in MHEE demonstrates the placebo treatment group, whose 9 out of 10 subjects discontinued with primary reason of EE Relapse. In the open-label LTS study, most subjects discontinued due to the withdrawal of consent (9-11%) or adverse event (7-11%).

The overall risk of discontinuation due to adverse event was relatively similar between treatment groups (1-4%). The most frequent adverse events leading to discontinuation among placebo were nausea, dyspepsia, and EE, whereas those among Dex were diarrhea and abdominal pain. [See Table 7.3.3.2].

**Table 7.3.3.2. Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug in ≥0.5% of Subjects in Phase 3 Studies<sup>1</sup>**

Preferred Term	Treatment Groups n (%)					
	Placebo (N=896)	Dexlansoprazole				Lanso 30 mg QD (N=1363)
		30 mg (N=455)	60 mg (N=2218)	90 mg (N=1754)	Total (N=4169)	
Diarrhea	1 (0.1%)	1 (0.2%)	16 (0.7%)	12 (0.7%)	29 (0.7%)	3 (0.2%)
Abdominal Pain @	2 (0.2%)	0	11 (0.5%)	10 (0.6%)	21 (0.5%)	4 (0.3%)
Nausea	7 (0.8%)	0	5 (0.2%)	5 (0.3%)	10 (0.2%)	1 (<0.1%)
Dyspepsia	7 (0.8%)	0	3 (0.1%)	1 (<0.1%)	4 (<0.1%)	0
Erosive Esophagitis	6 (0.7%)	0	1 (<0.1%)	0	1 (<0.1%)	0

<sup>1</sup> Adapted from sponsor's statistical table 3.2.3.1. Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug in Phase 3 Studies, from 4-Month Safety Update 2008 p.1549-1621.

@ includes abdominal pain, abdominal pain upper, and abdominal pain lower.

The incidence rates for adverse events leading to premature discontinuations were statistically significantly less among all three Dex treatment groups when compared to placebo. This is best demonstrated for symptoms of dyspepsia, nausea, and erosive esophagitis. [See Table 7.3.3.3.] No statistically significant differences were shown between the Dex and lansoprazole treatment groups.

**Table 7.3.3.3. Treatment-Emergent Adverse Events Leading to Premature Discontinuation Occurring in  $\geq 0.5$  Subject per 100 PM of Exposure in in All Phase 3 Studies<sup>1</sup>**

MedDRA HLT/ Preferred Term	Treatment Group n (rate per 100 patient-months of exposure)					
	Placebo (N=896)	Dex 30mg (N=455)	Dex 60mg (N=2311)	Dex 90mg (N=2142)	Dex Total (N=4548)	Lansoprazole 30mg (N=1363)
Total Subjects With $\geq 1$ Adverse Event	41 (3.86)	9 (0.96)*	78 (1.48)*	77 (1.29)*	164 (1.35)	18 (1.00)
<b>Dyspeptic Signs and Symptoms</b>	<b>8 (0.75)</b>	<b>0*</b>	<b>5 (0.09)*</b>	<b>1 (0.02)*</b>	<b>6 (0.06)</b>	<b>0</b>
Dyspepsia	7 (0.66)	0	3 (0.06)	1 (0.02)	4 (0.03)	0
Eructation	1 (0.09)	0	2 (0.04)	1 (0.02)	3 (0.02)	0
<b>Nausea and Vomiting Symptoms</b>	<b>7 (0.66)</b>	<b>1 (0.11)</b>	<b>9 (0.17)*</b>	<b>12 (0.29)*</b>	<b>22 (0.21)</b>	<b>3 (0.17)</b>
Nausea	7 (0.66)	0	6 (0.11)	9 (0.15)	15 (0.12)	1 (0.06)
Regurgitation	0	0	0	0	0	1 (0.06)
Vomiting	0	1 (0.11)	6 (0.11)	6 (0.10)	13 (0.11)	2 (0.11)
<b>Esophageal Ulcers and Perforation</b>	<b>6 (0.57)</b>	<b>0*</b>	<b>1 (0.02)*</b>	<b>0*</b>	<b>1 (&lt;0.01)</b>	<b>0</b>
Erosive Esophagitis	6 (0.57)	0	1 (0.02)	0	1 (<0.01)	0

<sup>1</sup> Sponsor's statistical table 3.2.7.1. Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug by Patient-Month of Exposure in Phase 3 Studies, from 5.3.5.4. 4-Month Safety Update pp.2442-2558.

\* Statistically significant difference when compared to placebo ( $p < 0.05$ )

In the HEE trials, the risk of discontinuation in the overall dexlansoprazole treatment group (1.9%) was slightly greater than lansoprazole (1.3%). This difference was not statistically significant. HEE study patients discontinued most frequently due to adverse events of abdominal pain and diarrhea.

In the MHEE trials, the risk of discontinuation in overall Dex treatment group (1.32 subjects/100PM) was higher than lansoprazole (0.89 subjects/100PM) and statistically significantly less than the placebo group (3.86 subjects/100PM). Patients discontinued most frequently due to adverse events of dyspepsia, EE, diarrhea, and nausea.

In the GERD trials, the risk of discontinuation in the overall dexlansoprazole treatment group was comparable to placebo, however, there was an increasing risk with increasing dose: 1.6% for 30mg, 2.9% for 60mg, and 3.6% for 90 mg dexlansoprazole. This difference was not statistically significant. GERD study patients discontinued most frequently due to adverse events of abdominal pain, nausea and vomiting, diarrhea, and headache.

In the LTS, the risk of premature discontinuation due to adverse event in the overall dexlansoprazole treatment group was 8.4%. Patients discontinued most frequently due to adverse events of diarrhea, abdominal pain, flatulence, bloating and distention, nausea and vomiting.

In Phase 1 Trials, a total of 10 subjects prematurely discontinued the study.

**Reviewer's Comments**

*The lower incidence rate of adverse events leading to premature discontinuations among the Dexlansoprazole treatment group, when compared to placebo, illustrates the therapeutic effect of the drug substance over placebo.*

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### 7.3.4 Significant Adverse Events

The sponsor conducted specially-focused analyses that acknowledged adverse events (AE) of public safety concern, related to the drug class (PPI), or suggested by results of dexlansoprazole trials. These analyses examined potential cardiovascular risk, hip/vertebral fracture and calcium homeostasis, hepatic enzyme abnormalities, gastric polyps, cholecystitis/cholelithiasis, respiratory tract infections (lower and upper), anemia and *C. difficile* diarrhea. The table below [Table 7.3.4.1] demonstrates the overall incidence rate of special interest AEs by treatment group in all Phase 3 trials.

**Table 7.3.4.1. Summary of Adverse Events of Special Interest in All Phase 3 Studies<sup>1</sup>**

Adverse Event Grouping	Treatment Group: n (rate per 100 PM)							
	Placebo (N=896) (Avg PM=1.2)	Dexlansoprazole						Lansoprazole 30 mg QD (N=1363) (Avg PM=1.3)
		30 mg QD (N=455) (Avg PM=2.1)	60 mg QD (N=2311) (Avg PM=2.3)	90 mg QD (N=1864) (Avg PM=2.2)	Updated <sup>a</sup> 90 mg QD (N=2142) (Avg PM=2.8)	Total (N=4270) (Avg PM=2.4)	Updated <sup>a</sup> Total (N=4548) (Avg PM=2.7)	
Potential Cardiovascular Events	19 (1.79)	18 (1.93)	85 (1.61)	58 (1.41)	71 (1.19)	160 (1.55)	173 (1.42)	31 (1.72)
Upper Respiratory Tract Infections	31 (2.92)	35 (3.75)	154 (2.92)	118 (2.88)	151 (2.53)	302 (2.93)	335 (2.75)	61 (3.39)
Lower Respiratory Tract Infections	5 (0.47)	5 (0.54)	18 (0.34)	12 (0.29)	18 (0.30)	35 (0.34)	41 (0.34)	7 (0.39)
Hepatic Enzymes Abnormalities	4 (0.38)	1 (0.11)	19 (0.36)	15 (0.37)	18 (0.30)	34 (0.33)	37 (0.30)	8 (0.44)
Cholelithiasis/Cholecystitis	1 (0.09)	0	3 (0.06)	4 (0.10)	5 (0.08)	7 (0.07)	8 (0.07)	2 (0.11)
Gastric Polyps	1 (0.09)	1 (0.11)	13 (0.25)	4 (0.10)	4 (0.07)	18 (0.17)	18 (0.15)	1 (0.06)
Hip and Vertebral Fracture and Calcium Homeostasis <sup>b</sup>	1 (0.09)	1 (0.11)	9 (0.17)	8 (0.19)	8 (0.13)	18 (0.17)	18 (0.15)	3 (0.17)
Anemia	2 (0.19)	1 (0.11)	11 (0.21)	7 (0.17)	9 (0.15)	19 (0.18)	21 (0.17)	3 (0.17)
<i>Clostridium difficile</i> Diarrhea	0	0	0	0	0	0	0	0

<sup>1</sup> Sponsor's Table 23 of 5.3.5.4. 4-Month Safety Update, p.77.

<sup>a</sup> Updated columns reflect new data added by LTS study in the 4-month safety update.

<sup>b</sup> No adverse events of hip or vertebral fractures were reported.

The special interest AEs as presented above, show no statistically significant differences of the incidence rate between any dexlansoprazole treatment group and lansoprazole 30mg or placebo. The added data from the 4-month safety update submission, increased the exposure time for the 90mg and total Dexlansoprazole treatment groups, thereby decreasing the previously reported incidence rates for all special interest AEs. Further discussion of these special interest AEs are examined below.

#### 7.3.4.1 Cardiovascular Risk

There were 281 potential cardiovascular (CV) AEs in 222 subjects reported by the sponsor as dizziness, shortness of breath, edema, syncope, chest pain/discomfort, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, other thromboembolic disorders, other coronary artery disorders, heart failures, arrhythmias, peripheral vascular disease, transient ischemic attack, hypertensive, and hypotensive disorders. The above Table 7.3.4.1 equates CV AE incidence in the placebo (1.79/100PM) and lansoprazole (1.72/100PM) treatment groups, while suggesting an overall lower incidence among the total Dexlansoprazole treatment group (1.42/100PM). When a single high level term (HLT), such as Ischemic Coronary Artery Disorders is examined, an incidence of 0.32/100PM for subjects on dexlansoprazole 30mg was statistically significant when compared to a zero incidence among those on lansoprazole 30mg. Other HLT groupings of Chest Pain, General Signs and Symptoms NEC (Chest Discomfort), and Heart Failures NEC continue to demonstrate an increased incidence of these AE in the Dexlansoprazole treatment group over its comparators, although not statistically significant. See the table below.

**Table 7.3.4.1.1. Selected Potential Cardiovascular Adverse Events in All Phase 3 Studies<sup>1</sup>**

MedDRA High Level Term Preferred Term	Treatment Group: n (rate per 100 PM)						
	Placebo (N=896) (Avg PM=1.2)	Dexlansoprazole					
		30 mg (N=455) (Avg PM=2.1)	60 mg (N=2311) (Avg PM=2.3)	ISS 90 mg (N=1864) (Avg PM=2.2)	Updated 90 mg (N=2142) (Avg PM=2.8)	ISS Total (N=4270) (Avg PM=2.4)	Updated Total (N=4548) (Avg PM=2.7)
<b>Total Subjects with ≥1 Adverse Event</b>	<b>19 (1.79)</b>	<b>18 (1.93)</b>	<b>85 (1.61)</b>	<b>58 (1.41)</b>	<b>71 (1.19)</b>	<b>160 (1.55)</b>	<b>173 (1.42)</b>
<b>Pain and Discomfort NEC</b>	<b>2 (0.19)</b>	<b>4 (0.43)</b>	<b>8 (0.15)</b>	<b>8 (0.19)</b>	<b>9 (0.15)</b>	<b>20 (0.19)</b>	<b>21 (0.17)</b>
Chest Pain	2 (0.19)	4 (0.43)	8 (0.15)	8 (0.19)	9 (0.15)	20 (0.19)	21 (0.17)
<b>Ischaemic Coronary Artery Disorders</b>	<b>0</b>	<b>3 (0.32)<sup>†</sup></b>	<b>2 (0.04)</b>	<b>1 (0.02)</b>	<b>1 (0.02)</b>	<b>6 (0.06)</b>	<b>6 (0.05)</b>
Acute Myocardial Infarction	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)
Angina Pectoris	0	1 (0.11)	0	0	0	1 (<0.01)	1 (<0.01)
Arteriospasm Coronary	0	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)
Myocardial Infarction	0	2 (0.21)	0	0	0	2 (0.02)	2 (0.02)
Myocardial Ischaemia	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)
<b>Heart Failures NEC</b>	<b>0</b>	<b>2 (0.21)</b>	<b>1 (0.02)</b>	<b>0</b>	<b>0</b>	<b>3 (0.03)</b>	<b>3 (0.02)</b>
Cardiac Failure	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)
Cardiac Failure Congestive	0	1 (0.11)	0	0	0	1 (<0.01)	1 (<0.01)
Cardiogenic Shock	0	1 (0.11)	0	0	0	1 (<0.01)	1 (<0.01)

MedDRA High Level Term Preferred Term	Treatment Group: n (rate per 100 PM)						
	Placebo (N=896) (Avg PM=1.2)	Dexlansoprazole					
		30 mg (N=455) (Avg PM=2.1)	60 mg (N=2311) (Avg PM=2.3)	ISS 90 mg (N=1864) (Avg PM=2.2)	Updated 90 mg (N=2142) (Avg PM=2.8)	ISS Total (N=4270) (Avg PM=2.4)	Updated Total (N=4548) (Avg PM=2.7)
<b>General Signs and Symptoms NEC</b>	<b>0</b>	<b>1 (0.11)</b>	<b>7 (0.13)</b>	<b>6 (0.15)</b>	<b>7 (0.12)</b>	<b>14 (0.14)</b>	<b>15 (0.12)</b>
Chest Discomfort	0	1 (0.11)	7 (0.13)	6 (0.15)	7 (0.12)	14 (0.14)	15 (0.12)
<b>Central Nervous System Haemorrhages and Cerebrovascular Accidents</b>	<b>0</b>	<b>1 (0.11)</b>	<b>0</b>	<b>1 (0.02)</b>	<b>1 (0.02)</b>	<b>2 (0.02)</b>	<b>2 (0.02)</b>
Cerebral Ischaemia	0	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)
Cerebrovascular Accident	0	1 (0.11)	0	0	0	1 (<0.01)	1 (<0.01)
<b>Coronary Artery Disorders NEC</b>	<b>1 (0.09)</b>	<b>0</b>	<b>1 (0.02)</b>	<b>2 (0.05)</b>	<b>2 (0.03)</b>	<b>3 (0.03)</b>	<b>3 (0.02)</b>
Coronary Artery Disease	1 (0.09)	0	1 (0.02)	2 (0.05)	2 (0.03)	3 (0.03)	3 (0.02)
Coronary Artery Occlusion	1 (0.09)	0	0	0	0	0	0
<b>Peripheral Embolism and Thrombosis</b>	<b>0</b>	<b>0</b>	<b>1 (0.02)</b>	<b>2 (0.05)</b>	<b>2 (0.03)</b>	<b>3 (0.03)</b>	<b>3 (0.02)</b>
Deep Vein Thrombosis	0	0	1 (0.02)	2 (0.05)	2 (0.03)	3 (0.03)	3 (0.02)
Thrombophlebitis Superficial	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)
<b>Pulmonary Thrombotic and Embolic Conditions</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.02)</b>	<b>1 (0.02)</b>	<b>1 (&lt;0.01)</b>	<b>1 (&lt;0.01)</b>
Pulmonary Embolism	0	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)
<b>Cerebrovascular Venous and Sinus Thrombosis</b>	<b>0</b>	<b>0</b>	<b>1 (0.02)</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.01)</b>	<b>1 (&lt;0.01)</b>
Cerebral Venous Thrombosis	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)
<b>Non-Site Specific Necrosis and Vascular Insufficiency NEC</b>	<b>0</b>	<b>0</b>	<b>1 (0.02)</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.01)</b>	<b>1 (&lt;0.01)</b>
Arteriosclerosis	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)
<b>Transient Cerebrovascular Events</b>	<b>0</b>	<b>0</b>	<b>1 (0.02)</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.01)</b>	<b>1 (&lt;0.01)</b>
Transient Ischaemic Attack	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)
<b>All Selected Cardiovascular AEs</b>	<b>3 (0.28)</b>	<b>11 (1.15)</b>	<b>23 (0.43)</b>	<b>21 (0.51)</b>	<b>23 (0.38)</b>	<b>54 (0.53)</b>	<b>57 (0.46)</b>

<sup>1</sup> From Sponsor's Table 24. Treatment-Emergent Potential Cardiovascular Adverse Events per 100 PM of Exposure in All Phase 3 Studies Combined, 5.3.5.4. 4-Month Safety Update, pp. 79-85.

<sup>†</sup> statistically significant when compared to lansoprazole 30mg.

The sponsor did focus on serious CV AEs of myocardial infarction, myocardial ischemia, unstable angina, cardiac-related death, and CVA to identify nine subjects across all 5 treatment groups. Subjects were characterized with mean age 55 years (range 23-71), male-to-female ratio 2:1, mean duration of treatment 54.3 days (range 1-213), majority of event onset <10 days after last dose of study drug, and all with a history of CV risk factors. Table 7.3.4.1.2. details these cases initially identified by the sponsor. All serious CV events were considered unrelated to study drug by the investigator. One subject, who suffered a CVA while on lansoprazole 30mg, subsequently developed hemiparesis which was considered possibly related to the study drug. No dose-response was shown. No cardiac-related deaths were reported in Phase 1 or Phase 3 studies.

**Table 7.3.4.1.2. Serious Cardiovascular Events in All Phase 3 Studies<sup>1</sup>**

Subject No. /Study	Age/ Sex	Event Day of Onset <sup>a</sup>	Duration of Treatment (Days)	Adverse Event (MedDRA Preferred Term)	Causality	Relevant Information
<b>Placebo</b>						
31989003/ T-GD05-137	56/ Female	25 (0)	25	Coronary Artery Occlusion	Not related	History of hypertension, asthma, hypercholesterolemia, atherosclerotic heart, syncope, prior myocardial infarction (2003). Multiple cardiovascular medications.
<b>Dexlansoprazole 30 mg QD</b>						
32454009/ T-GD05-137	71/ Female	27 (4) 30 (7)	23	Myocardial Infarction <sup>b</sup>	Not related	History of diabetes mellitus, hypertension, coronary artery disease, hyperlipidemia, peripheral vascular disease, prior carotid disease, prior carotid endarterectomy, non-drinker, ex-smoker. (Cardiovascular) medications included Avandia (since 1997)
				Cerebrovascular Accident	Not related	
9319002/ T-GD05-137	60/ Male	30 (2) 31 (3) 31 (3)	28	Myocardial Infarction Cardiogenic shock	Not related Not related	History of asthma, hypertension, sleep apnea, erectile dysfunction. Alternative etiology: atherosclerosis.
				Sepsis	Not related	
<b>Dexlansoprazole 60 mg QD</b>						
32849038/ T-EE04-085	67/ Male	47	62	Acute Myocardial Infarction	Not related	History of hypertension. Alternative etiology: heart disease.
7315029/ T-EE05-135	23/ Male	180 (1)	213 (34 lansoprazole 30 mg QD, 179 dexlansoprazole 60 mg QD)	Cerebral Venous Thrombosis <sup>b</sup>	Not related	History of headache, ethanol user, ex-tobacco, caffeine use. No history of transient ischemic attacks. Initial diagnosis of arterial malformation; subject recovered, but refused access to medical records.
32957001/ T-EE04-084	49/ Male	66 (0)	66	Coronary Artery Disease	Not related	History of atypical chest pain and retrosternal burning.
32118017/ T-EE04-084	51/ Male	1 (0)	1	Transient Ischemic Attack	Not related	History of coronary artery disease, hypertension, hyperlipidemia, diabetes, depression, cardiac arrhythmia. Multiple concomitant medications. Alternative etiology: preexisting condition.
<b>Dexlansoprazole 90 mg QD</b>						
18128038/ T-EE04-086	62/ Male	6 (1)	38 (33 dexlansoprazole 60 mg QD, 5 dexlansoprazole 90 mg QD)	Coronary Artery Disease	Not related	History of ischemic heart disease, hypertension, hypercholesterolemia, hyperglycemia, congestive heart failure, COPD, diabetes, post-infarction cardiomyopathy. Multiple concomitant medications. Alternative etiology: prior history of ischemic heart disease.
<b>Lansoprazole 30 mg QD</b>						
32713022/ T-EE04-084	56/ Female	42 (9)	33	Cerebrovascular Accident  Hemiparesis	Not related  Possible	History of sickle cell anemia, stroke with memory problems, subarachnoid hemorrhage, and mild schizotypal personality disorder.

<sup>1</sup> Sponsor's Table 2.7.q. from 2.7.4. Summary of Clinical Safety, pp. 57-8.

<sup>a</sup> Days postdosing in parentheses.

<sup>b</sup> Premature discontinuation of study drug.

In the 4-month safety update submission for this NDA, the sponsor again concluded that no greater incidence of potential CV AE were experienced by the Dex treatment group when compared to lansoprazole 30mg or placebo. The sponsor supported their conclusion with

(b) (4)

adjudication by cardiologist [See Table 7.3.4.1.4. in the Appendix for a listing of all 281 potential CV AE.] The cardiologist reviewed the 281 potential CV AE blinded to the assigned treatment groups and requested 39 for thorough assessment. Based on his final evaluation of the potential CV AEs, a new listing of 9 subjects were considered to have had true CV AEs based upon demographics, social and medical history, concomitant medications, and other related information. [See Table 7.3.4.1.3.] Six of these nine subjects were the same as those originally listed in the ISS. An additional 5 subjects were adjudicated with unconfirmed CV AEs due to lack of information to rule out cardiac origin of the AE.

**Table 7.3.4.1.3. Summary of Sponsor Adjudicated Confirmed Cardiovascular Events by PM of Exposure<sup>1</sup>**

Cardiovascular Adverse Events Category	Placebo (N=896) (Avg PM=1.2)	Dex 30 mg (N=455) (Avg PM=2.1)	Dex 60 mg (N=2311) (Avg PM=2.3)	Dex 90 mg (N=2142) (Avg PM=2.8)	Dex Total (N=4548) (Avg PM=2.7)	Lansoprazole 30 mg (N=1) (Avg PM=)
Number of Subjects with Cardiovascular Events	1 (0.09)	3 (0.32)	3 (0.06)	1 (0.02)	7 (0.06)	1 (0.06)
Nonfatal Myocardial Infarction	0	2 (0.21)	1 (0.02)	0	3 (0.02)	0
Angina	1 (0.09)	1 (0.11)	1 (0.02)	0	2 (0.02)	0
Chest Pain, Possibly Cardiac	0	0	1 (0.02)	1 (0.02)	2 (0.02)	0
Nonfatal Stroke	0	0	0	0	0	1 (0.06)

<sup>1</sup> Sponsor's Table 45 from 5.3.5.4. 4-Month Safety Update, p. 87.

**Reviewer's Comments:**

*This reviewer upon scrutiny of the incidence table of the 281 potential CV AE, saw that the lumping of data from nonspecific terms, such as dizziness, with major coronary events provided an inaccurate view of CV AE incidence and further analysis on the 281 potential CV AE was necessary. The major CV AE cases confirmed by sponsor's adjudication have hinted at an imbalance between Dexlansoprazole treatment groups and its comparators. Firstly, the incidence rate of the 30 mg Dexlansoprazole is 3-5x higher than that of its comparators. Secondly, ischemic coronary events, such as nonfatal MI and chest pain, have only occurred in the Dexlansoprazole treatment groups. The incidence table of all 281 potential CV AE [Table 7.3.4.1.4 in appendix] further demonstrates the perceived imbalance related to these 2 points. Within the HLT Ischaemic Coronary Artery Disorders, the 30mg Dexlansoprazole treatment group has a statistically significant incidence rate of 0.32/100PM when compared to 30mg lansoprazole's incidence rate of 0. This specified HLT grouping only has events occurring within the Dexlansoprazole treatment groups; none in placebo or lansoprazole. Looking at other specified HLT groupings of Chest Pain, General Signs and Symptoms NEC (Chest Discomfort), and Heart Failures NEC continue to demonstrate an increased incidence of these AE in the Dexlansoprazole treatment groups over its comparators. Interestingly, there was a reverse dose-related trend where incidence rate decreased with increasing dose of Dexlansoprazole. No convincing explanation can be found for this reverse trending.*

*An internal review was performed on the 281 potential CV AE. As noted for the sponsor's adjudicator, the process of qualifying a true CV AE was made challenging by the lack of adequate evidence to confirm cardiovascular etiology in many of these cases. Therefore, focusing on potential major CV AEs, 9 subjects were found to have likely cardiovascular events and 31 subjects with events considered indeterminable. Subjects with likely CV AEs are mean age  $57 \pm 9.6$  years (range 43-73), male 55%, median day of event onset  $31 \pm 38.9$  (range 2-152), 1/3 with onset 1-4 days after last dose of study drug, and all with a history of CV risk factors. These 9 subjects are listed below.*

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**Table 7.3.4.1.4. Reviewer Adjudicated Listing of Subjects with AE of Likely Cardiac Etiology**

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/MedDRA Preferred Term	Day of Onset	Durata	Alternative Etiology	Risk Factors				Tx Grp	
					Prior MI	HTN	DM	Col		Other
31989003/F/56/ T-GD05-137††	Coronary Artery Disorders NEC/ Coronary Artery Occlusion	25 (0)	3	Secondary to Type II diabetes, hypertension, and hypercholesterolemia	X	X	X	X	Shortness of Breath; Arteriosclerotic Heart Disease; Hypercholesterolemia; Mild Ischemia Anterior Wall; Syncope; Postmenopausal	Placebo
	Coronary Artery Disorders NEC/ Coronary Artery Disease	27 (0)	Ongoing (31)	“ “	X	X	X	“ “	“ “	Placebo
32454009/F/71/ T-GD05-137††	Heart Failures NEC/ Cardiac Failure Congestive	27 (4)	11	Myocardial Infarction		X	X	X	Coronary Artery Disease - Under Treatment; Peripheral Vascular Disease - Active; Hip Surgery - Left Hip Replacement; Endarterectomy Carotid Surgery	Dex 30 mg
	Ischemic Coronary Artery Disorders/Myocardial Infarction	27 (4)	20	Arteriosclerosis, secondary to hypertension and diabetes		X		X	“ “	Dex 30 mg
9319802/M/60/ T-GD05-137††	Ischemic Coronary Artery Disorders/Myocardial Infarction	30 (2)	30	Atherosclerosis		X			Bronchial Asthma; Pneumonia; Sleep Apnea; Erectile Dysfunction; Obesity; Immunoglobulin M Deficiency	Dex 30 mg
	Heart Failures NEC/Cardiogenic Shock	31(3)	29	Myocardial infarction		X			“ “	Dex 30 mg
32957001/M/49/ T-EE04-084†	Coronary Artery Disorders NEC/Coronary Artery Disease	66 (0)	10	Atherosclerosis coronary artery disease					Atypical Chest Pain and retrosternal pain	Dex 60 mg
	Cardiac Disorders NEC/Cardiac Disorder	47	Ong (65)	Ischemic heart disease		X			tobacco	Dex 60 mg
32849038/M/67/ T-EE04-085††	Ischemic Coronary Artery Disorders/ Acute Myocardial Infarction	47	5	Ischemic heart disease		X			“ “	Dex 60 mg

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPEDEX (Dexlansoprazole)

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/MedDRA Preferred Term	Day of Onset	Durata	Alternative Etiology	Risk Factors				Tx Grp	
					Prior MI	HTN	DM	Chol		Other
	Heart Failures NEC/Cardiac Failure	47	Ong (65)	Coronary heart disease	X				“ “	Dex 60 mg
	Arteriosclerosis Obliterans	47	Ong (65)	Atherosclerosis	X				“ “	Dex 60 mg
3000009/F/43/ T-EE04-085	Ischemic Coronary Artery Disorders/Arteriospasm Coronary	31	3	Known cardiac arrhythmia					Cardiac Arrhythmia - Type of Arrhythmia Unknown; Cardiac Catheterization; Prolapsed Mitral Valve; Vasovagal Nerve Problems; Grade A Reflux Esophagitis;	Dex 90 mg
1812803/M/62/ T-EE04-086†	Coronary Artery Disorders NEC/ Coronary Artery Disease	6 (1)	3	Past history of coronary artery disease	X		X	X	Congestive Heart Failure; Chronic Obstructive Pulmonary Disease; Ischemic Heart Disease; Postmyocardial Infarction Cardiomyopathy; Hiatal Hernia Per Screening EGD; Stent Placement; Intermittent Rectal Bleeding	Dex 90 mg
32446005/F/45/ T-EE04-087†	Pain and Discomfort NEC/ Chest Pain	2	15	Past history of coronary artery disease	X		X	X	“ “	Dex 90 mg
8097056/M/60/ T-EE05-135	Ischemic Coronary Artery Disorders/Myocardial Ischemia	119 (0)	6	Anxiety		X				Dex 60mg
	Ischemic Coronary Artery Disorders/Angina Pectoris	152 (0)	10min	Coronary Artery Disease		X	X	X	Coronary Artery Disease; Neuropathy; Bronchitis; COPD; Sleep Apnea; Chest Pain; Hiatal Hernia; Coronary Triple Vessel Bypass Graft; Obesity	Dex 30mg

† identified in original ISS

‡ identified in sponsor's adjudication

*This internal review finds the same pattern of increased CV AE cases among the Dexlansoprazole treatment groups and the statistically significant 5.6x greater incidence among the 30mg Dexlansoprazole when compared to lansoprazole. Of the potential CV AEs with likely or indeterminable cardiac etiology, approximately half (46%) occurred in subjects with medical history and/or risk factors that may have contributed to the CV AE. Although the study was not designed to control for baseline cardiovascular risk factors, the sponsor supports the fact that these risk factors were equally distributed among all 5 treatment groups of the Phase 3 studies. See table below.*

**Table 7.3.4.1.5. Baseline Cardiovascular Risk Factors in Phase 3 Studies<sup>1\*</sup>**

Table 1.1.1 Baseline Cardiovascular Risk Factors in Phase 3 Studies							
Cardiovascular Risk Factors	Placebo (N=896)	TAK-390MR 30 mg (N=455)	TAK-390MR 60 mg (N=2311)	TAK-390MR 90 mg (N=2162)	TAK-390MR Total (N=4549)	Lanso 30 mg QD (N=1363)	All Subjects (N=6225)
Subjects with at Least One Cardiovascular Risk Factor	717 (80%)	364 (80%)	1851 (80%)	1693 (79%)	3609 (79%)	1082 (79%)	4917 (79%)
Subjects with at Least One Medical History Risk Factor	406 (45%)	224 (49%)	1042 (45%)	932 (44%)	2028 (45%)	582 (43%)	2753 (44%)
Myocardial Infarction	12 (1%)	5 (1%)	18 (1%)	15 (1%)	34 (1%)	10 (1%)	55 (1%)
Coronary Artery Disease	19 (2%)	11 (2%)	53 (2%)	41 (2%)	95 (2%)	27 (2%)	131 (2%)
Myocardial Ischemia	4 (<1%)	2 (<1%)	3 (<1%)	3 (<1%)	7 (<1%)	6 (<1%)	14 (<1%)
Angina	16 (2%)	4 (<1%)	24 (1%)	18 (<1%)	42 (<1%)	7 (<1%)	57 (<1%)
Coronary Artery Bypass Graft	3 (<1%)	3 (<1%)	16 (<1%)	10 (<1%)	26 (<1%)	4 (<1%)	33 (<1%)
PTCA (Angioplasty)	11 (1%)	4 (<1%)	25 (1%)	18 (<1%)	42 (<1%)	6 (<1%)	52 (<1%)
Cerebrovascular Accident	5 (<1%)	3 (<1%)	9 (<1%)	9 (<1%)	18 (<1%)	10 (<1%)	29 (<1%)
TIA/Reversible Ischemic Neurological Deficit	6 (<1%)	3 (<1%)	14 (<1%)	9 (<1%)	22 (<1%)	9 (<1%)	34 (<1%)
Hypertension	224 (25%)	124 (27%)	636 (28%)	563 (26%)	1222 (27%)	345 (25%)	1642 (26%)
Venous Thrombotic Events (DVT/PE)	4 (<1%)	1 (<1%)	6 (<1%)	6 (<1%)	13 (<1%)	5 (<1%)	18 (<1%)
Peripheral Vascular Disease	4 (<1%)	2 (<1%)	20 (<1%)	11 (<1%)	31 (<1%)	8 (<1%)	39 (<1%)
Congestive Heart Failure	4 (<1%)	1 (<1%)	8 (<1%)	4 (<1%)	11 (<1%)	4 (<1%)	17 (<1%)
Cardiac Arrhythmia	26 (3%)	15 (3%)	50 (2%)	56 (3%)	107 (2%)	41 (3%)	153 (2%)
Valvular Heart Disease	26 (3%)	10 (2%)	46 (2%)	48 (2%)	92 (2%)	21 (2%)	132 (2%)
Atherosclerotic Disease	3 (<1%)	5 (1%)	8 (<1%)	6 (<1%)	19 (<1%)	1 (<1%)	23 (<1%)
Hyperlipidemia	228 (25%)	125 (28%)	582 (25%)	506 (24%)	1121 (25%)	318 (23%)	1513 (24%)
Diabetes	64 (7%)	37 (8%)	128 (6%)	120 (6%)	265 (6%)	66 (5%)	356 (6%)
Other CV Risks	27 (3%)	24 (5%)	76 (3%)	65 (3%)	149 (3%)	38 (3%)	198 (3%)
Subjects with at Least One Life Style Risk Factor	614 (69%)	307 (67%)	1581 (68%)	1446 (68%)	3073 (68%)	943 (69%)	4190 (67%)
BMI >= 30	374 (42%)	184 (40%)	968 (42%)	891 (42%)	1980 (42%)	569 (42%)	2551 (42%)
Smoking	396 (44%)	209 (46%)	1040 (45%)	998 (47%)	2073 (46%)	643 (47%)	2819 (45%)
Any Cardiovascular Risk Factors							
1-2 Risk Factors	533 (59%)	259 (57%)	1360 (59%)	1239 (59%)	2643 (59%)	923 (60%)	2635 (58%)
3-4 Risk Factors	146 (16%)	86 (19%)	416 (18%)	391 (18%)	824 (18%)	217 (16%)	1079 (17%)
>=5 Risk Factors	38 (4%)	19 (4%)	75 (3%)	63 (3%)	142 (3%)	42 (3%)	203 (3%)
Any Medical History Risk Factors							
1-2 Risk Factors	340 (38%)	189 (42%)	883 (38%)	791 (37%)	1722 (38%)	502 (37%)	2338 (38%)
3-4 Risk Factors	51 (6%)	19 (4%)	138 (6%)	129 (6%)	271 (6%)	69 (5%)	360 (6%)
>=5 Risk Factors	15 (2%)	6 (1%)	21 (<1%)	12 (<1%)	35 (<1%)	11 (<1%)	55 (<1%)
Any Life Style Risk Factors							
1-2 Risk Factors	614 (69%)	307 (67%)	1581 (68%)	1446 (68%)	3073 (68%)	943 (69%)	4190 (67%)
Studies included: T-CD04-082, T-CD04-083, T-CD05-137, T-EE04-084, T-EE04-085, T-EE04-086, T-EE04-087, T-EE05-135, and T-GE04-088.							
Subjects enrolled in more than one study may have received different study drugs and are counted in more than one treatment group.							

<sup>1</sup>From Response to FDA Request August 13, 2008 to TAP Pharmaceuticals, Inc.

\*TAK-390MR = Dexlansoprazole

*A review of cardiovascular AE risk was performed by the FDA's Office of Surveillance and Epidemiology (OSE), Dr. Wysowski. OSE focused on the 9 subjects with major CV AE that could be confirmed by the available data, and concluded that Dexlansoprazole was not likely a cause of cardiovascular disorders in the Phase 3 clinical studies. However, based on data from*

*the U.S. National Hospital Discharge Survey, the rate of nonfatal myocardial infarction in the dexlansoprazole 30mg group of 0.21/100 PM is 10 times the expected number of 0.02 per 100PM, whereas the rates in the Dex treatment groups are consistent with the expected number.*

*Considering that most of the general population taking PPIs regularly have  $\geq 1$  cardiovascular risk factor and are so indicated for treatment of symptomatic GERD, the increased incidence of major CV AEs among the Dexlansoprazole 30mg subjects (dosage proposed for symptomatic GERD) over lansoprazole subjects, cannot be dismissed. It is, however, notable that the 60mg and 90mg Dex dosages did not demonstrate such concern. Recommendations to revise the "Adverse Reactions" section of the Dex labeling will address the concern for myocardial infarction and chest pain in the Dex population.*

#### 7.3.4.2 Hip and Vertebral Fracture and Calcium Homeostasis

There were no statistically significant differences between any dexlansoprazole treatment group and lansoprazole 30mg or placebo for bone and calcium homeostasis AEs. No hip fractures or vertebral fractures AEs were reported in any Phase 3 or Phase 1 studies. Two subjects were reported with osteoporosis; one each in the dexlansoprazole 60mg and 90mg treatment group. Two subjects were reported with osteopenia; one each in the dexlansoprazole 60mg and 90mg treatment groups. These events occurred in postmenopausal women, aged  $\geq 55$  years, and were considered nonserious. Lastly, no changes in mean calcium were clinically significant and remained consistent during the Phase 3 studies.

#### **Reviewer's Comments:**

*Although there were no hip or vertebral fractures demonstrated in the development program of Dexlansoprazole, there was an increased number of falls and other fractures among the Dexlansoprazole treatment groups when compared to placebo and 30mg lansoprazole treatment groups. The overall incidence rate of the total Dexlansoprazole population, however, was not dissimilar to that of lansoprazole. A summary of all serious and non-serious falls and/or fractures is presented in the table below.*

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**Table 7.3.4.2.1. Bone Fracture and Fall Adverse Events by PM Exposure in all Phase 3 Studies<sup>1</sup>**

Fractures/Falls	Placebo	Dex 30 mg	Dex 60 mg	Updated Dex 90 mg	Updated Total Dex	Lanso 30 mg QD
MedDRA High Level Term/	(N=896)	(N=455)	(N=2311)	(N=2142)	(N=4548)	(N=1363)
Preferred Term	(Avg.PM=1.2)	(Avg.PM=2.1)	(Avg.PM=2.3)	(Avg.PM=2.8)	(Avg.PM=2.7)	(Avg.PM=1.3)
Total Subjects with at Least One Adverse Event	1 (0.09)	3 (0.31)	14 (0.26)	7 (0.12)	25 (0.20)	4 (0.23)
<b>LOWER LIMB FRACTURES AND DISLOCATIONS</b>	<b>1 (0.09)</b>	<b>0</b>	<b>2 (0.04)</b>	<b>2 (0.03)</b>	<b>4 (0.03)</b>	<b>2 (0.11)</b>
ANKLE FRACTURE	0	0	1 (0.02)	1 (0.02)	2 (0.02)	0
FOOT FRACTURE	1 (0.09)	0	0	0	0	2 (0.11)
PATELLA FRACTURE	0	0	1 (0.02)	0	1 (<0.01)	0
TIBIA FRACTURE	0	0	0	1 (0.02)	1 (<0.01)	0
<b>THORACIC CAGE FRACTURES AND DISLOCATIONS</b>	<b>0</b>	<b>1 (0.11)</b>	<b>2 (0.04)</b>	<b>1 (0.02)</b>	<b>4 (0.03)</b>	<b>0</b>
RIB FRACTURE	0	1 (0.11)	2 (0.04)	1 (0.02)	4 (0.03)	0
<b>UPPER LIMB FRACTURES AND DISLOCATIONS</b>	<b>0</b>	<b>0</b>	<b>4 (0.08)</b>	<b>3 (0.05)</b>	<b>7 (0.06)</b>	<b>1 (0.06)</b>
CLAVICLE FRACTURE	0	0	0	1 (0.02)	1 (<0.01)	0
HAND FRACTURE	0	0	1 (0.02)	1 (0.02)	2 (0.02)	0
ULNA FRACTURE	0	0	0	1 (0.02)	1 (<0.01)	0
UPPER LIMB FRACTURE	0	0	3 (0.06)	1 (0.02)	4 (0.03)	0
WRIST FRACTURE	0	0	0	1 (0.02)	1 (<0.01)	1 (0.06)
<b>NON-SITE SPECIFIC INJURIES NEC</b>	<b>0</b>	<b>3</b>	<b>8</b>	<b>5</b>	<b>16</b>	<b>1</b>
FALL	0	3	8	5	16	1
<b>Total Fracture/Fall Events</b>	<b>1 (0.09)</b>	<b>4 (0.42)</b>	<b>16 (0.30)</b>	<b>11 (0.18)</b>	<b>31 (0.25)</b>	<b>4 (0.23)</b>

<sup>1</sup> Reviewer's Table. Adapted from Sponsor's Statistical Table 3.7.7.8.1. of 5.3.5.3.Integrated Summary of Safety, Statistical Table 3.3.3.8.1 of 5.3.5.4. 4-Month Safety Update, Nonfatal Serious Adverse Event Listing of 5.3.5.3.Integrated Summary of Safety pp.142-147, and from Sponsor's Response to FDA Request August 13, 2008.

*Further examination of all serious and non-serious injury-related AEs again shows an imbalance where the incidence rate for Dexlansoprazole treatment group is greater than that of its comparators, as was discussed in Section 7.3.2 Serious Adverse Events. The incidence rate among placebo and lansoprazole are similar, at 0.37 and 0.40/100PM, respectively, compared to that of 0.67/100PM for the total Dexlansoprazole population. No dose-related trend is demonstrated. This analysis is presented in the following table.*

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**Table 7.3.4.2.2. Reviewer's Table of Serious and Nonserious Injury AEs in all Phase 3 Studies<sup>1\*</sup>**

SERIOUS AND NONSERIOUS INJURY AEs  MedDRA High Level Term Preferred Term	Treatment Group: n (rate per 100 PM)					
	Placebo (N=896) (Avg. PM=1.2)	Dexlansoprazole				Lansoprazole 30 mg QD (N=1363) (Avg. PM=1.3)
		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)	
Non-Site Specific Injuries NEC	0	5	13	5	23	2
Fall	0	3	8	4	15	1
Foreign Body Trauma	0	0	1	0	1	0
Road Traffic Accident	0	1	2	0	3	1
Wound	0	0	0	1	1	0
Injury	0	1	2	0	3	0
Disturbances In Consciousness NEC	0	0	1	1	2	0
Inner Ear Signs and Symptoms	0	0	0	1	1	0
Lower Limb Fractures and Dislocations	1	0	2	2	4	2
Muscle, Tendon and Ligament Injuries	0	0	5	3	8	1
Musculoskeletal and Connective Tissue Signs and Symptoms NEC	0	0	0	1	1	0
Thoracic Cage Fractures and Dislocations	0	1	2	1	4	0
Upper Limb Fractures and Dislocations	0	0	4	3	7	1
Limb Injuries NEC (Incl Traumatic Amputation)	2	3	12	7	22	0
Site Specific Injuries NEC	1	2	4	3	9	1
Intervertebral Disc Disorders NEC	0	0	0	2	2	0
Joint Related Disorders NEC	0	0	0	1	1	0
<b>Total: n</b>	<b>4</b>	<b>11</b>	<b>41</b>	<b>30</b>	<b>82</b>	<b>7</b>
<b>Incidence rate (subjects per 100 PM) (95% CI)</b>	<b>0.37 (0.12, 0.90)</b>	<b>0.12 (0.06, 0.20)</b>	<b>0.77 (0.56, 1.04)</b>	<b>0.50 (0.34, 0.71)</b>	<b>0.67 (0.53, 0.82)</b>	<b>0.40 (0.17, 0.78)</b>
<b>Rate Ratio compared to Placebo<sup>†</sup> (95% CI)</b>	<b>--</b>	<b>3.1 (1.0, 11.2)</b>	<b>2.1 (0.8, 6.8)</b>	<b>1.3 (0.5, 4.5)</b>	<b>1.8 (0.7, 5.8)</b>	<b>1.1 (0.3, 4.1)</b>
<b>Rate Ratio compared to Lansoprazole<sup>†</sup> (95% CI)</b>	<b>0.9 (0.2, 3.3)</b>	<b>2.9 (1.1, 8.0)</b>	<b>2.0 (0.9, 4.7)</b>	<b>1.3 (0.6, 3.1)</b>	<b>1.7 (0.8, 4.0)</b>	<b>--</b>

<sup>1</sup> Adapted from Sponsor's Statistical Table 3.7.7.8.1. of 5.3.5.3. Integrated Summary of Safety, Statistical Table 3.3.3.8.1 of 5.3.5.4. 4-Month Safety Update, Nonfatal Serious Adverse Event Listing of 5.3.5.3. Integrated Summary of Safety pp. 142-147, and from Sponsor's Response to FDA Request August 13, 2008.

\*Events with preferred terms of excoriation, arthropod bite or sting, and auditory hallucination were excluded.

<sup>†</sup> calculated using the OpenEpi Collection of Epidemiologic Calculators. Version 2.2.1. Updated 4/5/2008.

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*The current medical literature reports increased risk of hip fracture associated with long-term PPI use. These observational studies have demonstrated 44% increased risk with >1 year of use to almost 5x increased risk with >7 years of PPI use. (Yang 2006, Targownik 2008). Of all*

participants in the Dexlansoprazole Phase 3 studies, 44-48% of subjects averaged 24.0-28.3 months on PPIs prior to enrollment. Examining medical records of subjects experiencing  $\geq 1$  injury-related AE, the average prior PPI exposure was 17.5-26.3 months for all treatment groups except placebo. The placebo treatment group had prior PPI exposure of 49.2 months, however, only 2 subjects in this group had prior PPI use. Unfortunately, an apparent association between increased length of PPI exposure and increased risk of fracture or injury-related AE is difficult to conclude from the data provided.

The imbalance of injury-related AEs in the Dexlansoprazole treatment population compared to placebo and lansoprazole treatment groups discussed here and among the SAEs (Section 7.3.2), indicates that further study is needed to explain injury-related risks.

### 7.3.4.3 Hepatic Enzyme Abnormalities

As shown in Table 7.3.4.1., no statistically significant difference in overall incidence rates was found between any dexlansoprazole treatment group and the control groups. Increased AST and abnormal liver function tests were the most frequently reported in the placebo treatment group, while increased ALT was most frequent in the Dexlansoprazole and lansoprazole treatment groups. Dexlansoprazole displayed an increasing dose-related trend for incidence of ALT increased (0.11, 0.19, and 0.24/100 PM for 30-mg, 60-mg, and 90-mg Dexlansoprazole treatment groups, respectively). There were 49 patients in all Phase 3 studies with liver enzyme abnormalities.

Table 7.3.4.3.1 Hepatic Enzyme Abnormality Adverse Events in All Phase 3 Studies<sup>1</sup>

MedDRA High Level Term Preferred Term	Treatment Group: n (rate per 100 PM)							
	Placebo (N=396) (Avg PM=1.2)	30 mg QD (N=455) (Avg PM=2.1)	60 mg QD (N=2311) (Avg PM=2.3)	Dexlansoprazole MR				Lansoprazole 30 mg QD (N=1363) (Avg PM=1.3)
				90 mg QD		Total Dexlansoprazole MR		
				ISS 90 mg QD (N=1864) (Avg PM=2.2)	Update 90 mg QD (N=2142) (Avg PM=2.8)	ISS Total (N=4270) (Avg PM=2.4)	Update Total (N=4548) (Avg PM=2.7)	
Total Subjects With $\geq 1$ Adverse Event	4 (0.38)	1 (0.11)	19 (0.36)	15 (0.37)	18 (0.30)	34 (0.33)	37 (0.30)	8 (0.44)
Liver Function Analyses	4 (0.38)	1 (0.11)	19 (0.36)	14 (0.34)	17 (0.28)	33 (0.32)	36 (0.30)	8 (0.44)
Alanine Aminotransferase Increased	1 (0.09)	1 (0.11)	10 (0.19)	10 (0.24)	11 (0.18)	20 (0.19)	21 (0.17)	4 (0.22)
Aspartate Aminotransferase Increased	2 (0.19)	0	5 (0.09)	5 (0.15)	5 (0.13)	11 (0.11)	13 (0.11)	3 (0.17)
Blood Bilirubin Increased	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)	0
Hepatic Enzyme Increased	0	0	4 (0.03)	2 (0.05)	3 (0.05)	6 (0.06)	7 (0.06)	2 (0.11)
Liver Function Test: Abnormal	2 (0.19)	0	3 (0.06)	2 (0.05)	2 (0.03)	5 (0.05)	5 (0.04)	0
Transaminases Increased	0	0	2 (0.04)	0	0	2 (0.02)	2 (0.02)	0
Tissue Enzyme Analyses NEC	0	0	2 (0.04)	2 (0.05)	2 (0.03)	3 (0.03)	3 (0.02)	1 (0.06)
Blood Alkaline Phosphatase Increased	0	0	2 (0.04)	2 (0.05)	2 (0.03)	3 (0.03)	3 (0.02)	1 (0.06)

<sup>1</sup> Sponsor's Table 30 of 5.3.5.4. 4-Month Safety Update, p. 101.

Six subjects had levels  $\geq 3x$  ULN of AST or ALT (1 placebo, 3 dexlansoprazole MR 60 mg QD, 2 dexlansoprazole MR 90 mg QD). There were no subjects with simultaneous elevations of AST and ALT and total bilirubin, no subjects with  $\geq 10x$  ULN for hepatic enzymes, no Hy's law cases and no cases of hepatic failure.

#### 7.3.4.4 Gastric Polyps

The reporting of gastric polyps was dependent on investigator and endoscopy frequency varied by study indication and treatment group. Nonetheless, the incidence of treatment-emergent gastric polyp AE per 100 endoscopies was similar (0.3-0.5) among placebo, dexlansoprazole 30mg and 60mg treatment groups. The dexlansoprazole 90mg and lansoprazole 30mg treatment groups both had a reported gastric polyp AE incidence <0.1/100 endoscopies. No statistically significant difference in overall incidence rates was found between any dexlansoprazole treatment group and the control groups. No dose response shown.

Half of gastric polyps reported in the HEE studies and the majority of gastric polyps in MHEE studies were considered treatment-related. For both of these study indications, the highest incidence rate of gastric polyps occurred in the dexlansoprazole 60mg treatment group.

#### Reviewer's Comment

*This highest incidence of gastric polyps in the Dex 60mg treatment cannot be explained as the treatment group did not demonstrate the highest serum gastrin levels or significant histologic changes upon endoscopy.*

#### 7.3.4.5 Cholecystitis/Cholelithiasis

No statistically significant difference in overall incidence rates was found between any dexlansoprazole treatment group and the control groups. There were 5 SAE of cholecystitis and/or cholelithiasis also reported during screening period before exposure to study drug.

#### 7.3.4.6 Upper Respiratory Tract Infections

No statistically significant difference in overall incidence rates was found between any dexlansoprazole treatment group and the control groups. No dose response was shown for the incidence of any specific upper respiratory tract infections (URI). However, in Symptomatic GERD studies, there is a statistically significant increased risk of URI among subjects on dexlansoprazole 90mg (7.9%) when compared to the placebo (2.6%), dexlansoprazole 30mg (3.5%) and 60mg (3.7%) treatment groups. Most subjects reporting URIs had a history of seasonal allergies, asthma, or bronchitis.

#### 7.3.4.7 Lower Respiratory Tract Infections

No statistically significant difference in overall incidence rates for lower respiratory tract infections (LRI) was found between any dexlansoprazole treatment group and the control groups. No dose response was shown for the incidence of any specific LRI.

Three subjects experienced pneumonia; two on dexlansoprazole 60mg (HEE #32457009, LTS #9172011) and one on lansoprazole 30mg (HEE #32471003).

#### 7.3.4.8 Anemia

No statistically significant difference in overall incidence rates for anemia was found between any dexlansoprazole treatment group and the control groups. No dose response shown.

#### 7.3.4.9 *Clostridium difficile* Diarrhea

No AEs were reported in this category.

### 7.3.5 Submission Specific Primary Safety Concerns

#### 7.3.5.1 Long Term Safety Concerns

In the LTS study, adverse event incidence rates were highest during the first 3 months of the study, decreasing and remaining constant during the remaining nine months. Adverse events reported in  $\geq 5\%$  of subjects (URIs, Gastrointestinal/Abdominal Pains, Diarrhea, Nausea/Vomiting, Headaches NEC, and Flatulence, Bloating and Distention) occurred within the first 3 months of the study. URIs were the most frequently reported adverse event (14.4%), however, there were also frequent musculoskeletal and connective tissue AEs in the LTS. [See Section 7.4.1. for more discussion on common AEs.] Three deaths occurred and, as described above in Section 7.3.1, none were considered study drug related. Seven SAEs occurred that were considered possibly study drug related, mentioned above in Section 7.3.2. Premature discontinuations were mainly due to adverse events of diarrhea, abdominal pain, nausea and vomiting.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The most frequently reported adverse events occurred at an incidence in  $\geq 1$  subject/100PM and were diarrhea, upper respiratory tract infections (URI), gastrointestinal and abdominal pains, nausea and vomiting, headaches, and flatulence, bloating and distension. The overall incidence rate of these common AEs were statistically significantly lower for subjects given doses of Dexlansoprazole than those who received placebo or lansoprazole. These common AEs were similar in the Dexlansoprazole and lansoprazole treatment groups, with the addition of diaphragmatic hernias, and gastrointestinal atonic and hypomotility disorders. The lansoprazole MR treatment group had a statistically significantly higher incidence of flatulence, bloating and distention (than 60mg and 90mg Dex) and hiatal hernia (than 30mg and 60mg Dex). Placebo demonstrated a similar list of common AEs with the addition of dyspepsia and gastrointestinal atonic and hypomotility disorders. The placebo treatment group had a statistically significantly higher incidence of headache (than each dose of Dex), general

abdominal pain (than 60mg Dex), dyspepsia (than 60mg and 90mg Dex), and GI atonic/hypomotility disorders (than 30mg and 90mg Dex). No dose-related trend was observed.

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**Table 7.4.1.1. Treatment-Emergent Adverse Events Experienced by ≥1 Subject per 100 PM of Exposure in Any Treatment Group in All Phase 3 Studies<sup>1,2</sup>**

	Treatment Group: n (rate per 100 PM)					
	Placebo (N=896) (Avg PM=1.2)	30 mg (N=455) (Avg PM=2.1)	60 mg (N=2311) (Avg PM=2.3)	Dexlansoprazole 90 mg (N=1864) (Avg PM=2.2)	Total (N=4270) (Avg PM=2.4)	Lansoprazole 30 mg (N=1363) (Avg PM=1.3)
<b>MedDRA High Level Term Preferred Term</b>						
Total Subjects With ≥1 Adverse Event	260 (24.49)	175 (18.75)*	874 (16.59)*†	642 (15.64)*†	1618 (15.70)	379 (21.06)
Headaches NEC	38 (3.58)	16 (1.71)*	79 (1.50)*	69 (1.68)*	164 (1.59)	32 (1.78)
Headache	35 (3.30)	14 (1.50)	71 (1.35)	64 (1.56)	149 (1.45)	29 (1.61)
Sinus Headache	1 (0.09)	2 (0.21)	2 (0.04)	5 (0.12)	9 (0.09)	2 (0.11)
Tension Headache	2 (0.19)	0	6 (0.11)	2 (0.05)	8 (0.08)	1 (0.06)
<b>Gastrointestinal and Abdominal Pains (Excl Oral and Throat)</b>						
Abdominal Pain	31 (2.92)	16 (1.71)	98 (1.86)*	82 (2.00)	195 (1.89)	35 (1.94)
Abdominal Pain Lower	10 (0.94)	6 (0.64)	44 (0.84)	40 (0.97)	90 (0.87)	16 (0.89)
Abdominal Pain Upper	5 (0.47) 4	3 (0.32)	13 (0.25)	9 (0.22)	25 (0.24)	3 (0.17)
Abdominal Tenderness	14 (1.32)	5 (0.54)	32 (0.61)	27 (0.66)	64 (0.62)	11 (0.61)
Gastrointestinal Pain	0	0	10 (0.19)	6 (0.15)	21 (0.20)	4 (0.22)
Oesophageal Pain	1 (0.09)	0	1 (0.02)	0	1 (<0.01)	2 (0.11)
<b>Upper Respiratory Tract Infections</b>						
Acute Sinusitis	22 (2.07)	25 (2.68)	99 (1.88)	81 (1.97)	200 (1.94)	36 (2.00)
Laryngitis	0	1 (0.11)	2 (0.04)	0	3 (0.03)	0
Nasopharyngitis	8 (0.75)	7 (0.75)	23 (0.44)	18 (0.44)	48 (0.47)	16 (0.89)
Pharyngitis	4 (0.38)	0	5 (0.09)	2 (0.05)	7 (0.07)	2 (0.11)
Rhinitis	0	0	0	1 (0.02)	1 (<0.01)	2 (0.11)
Sinusitis	5 (0.47)	4 (0.43)	20 (0.38)	26 (0.63)	49 (0.48)	4 (0.22)
Tonsillitis	1 (0.09)	0	5 (0.09)	0	5 (0.05)	1 (0.06)
Upper Respiratory Tract Infection	7 (0.66)	13 (1.39)	50 (0.95)	36 (0.88)	98 (0.95)	11 (0.61)
<b>Nausea and Vomiting Symptoms</b>						
Nausea	27 (2.54)	21 (2.25)	92 (1.75)	73 (1.78)	185 (1.79)	36 (2.00)
Regurgitation	23 (2.17)	15 (1.61)	71 (1.35)	48 (1.17)	133 (1.29)	24 (1.33)
Retching	0	0	1 (0.02)	1 (0.02)	2 (0.02)	2 (0.11)
Vomiting	2 (0.19)	0	2 (0.04)	2 (0.05)	4 (0.04)	0
<b>Diarrhoea (Excl Infective)</b>						
Diarrhoea	7 (0.66)	10 (1.07)	35 (0.66)	36 (0.88)	81 (0.79)	15 (0.83)
<b>Flatulence, Bloating and Distension</b>						
Abdominal Distension	26 (2.45)	23 (2.46)	121 (2.30)	85 (2.07)	227 (2.20)	44 (2.44)
Flatulence	26 (2.45)	23 (2.46)	121 (2.30)	85 (2.07)	227 (2.20)	44 (2.44)
	12 (1.13)	14 (1.50)	59 (1.12)†	40 (0.97)†	113 (1.10)	32 (1.78)
	9 (0.85)	3 (0.32)	30 (0.57)	23 (0.56)	56 (0.54)	18 (1.00)
	5 (0.47)	12 (1.29)	33 (0.63)	19 (0.46)	64 (0.62)	16 (0.89)

<b>Byssopic Sogas and Symptoms</b>													
Dyspepsia	16 (1.51)	7 (0.75)	17 (0.32)*	9 (0.22)*	33 (0.32)	6 (0.33)							
Epigastric Discomfort	12 (1.13)	4 (0.43)	11 (0.21)	4 (0.10)	19 (0.18)	2 (0.11)							
Eructation	1 (0.09)	1 (0.11)	0	0	1 (<0.01)	1 (0.06)							
	3 (0.28)	3 (0.32)	6 (0.11)	5 (0.12)	14 (0.14)	3 (0.17)							
<b>Gastrointestinal Atonic and Hypomotility Disorders NEC</b>													
Constipation	16 (1.51)	5 (0.54)*	47 (0.89)	25 (0.61)*	77 (0.75)	20 (1.11)							
Gastroesophageal Reflux Disease	11 (1.04)	4 (0.43)	34 (0.65)	21 (0.51)	59 (0.57)	15 (0.83)							
Impaired Gastric Emptying	5 (0.47)	1 (0.11)	8 (0.15)	3 (0.07)	12 (0.12)	4 (0.22)							
Infrequent Bowel Movements	0	0	2 (0.04)	2 (0.05)	4 (0.04)	1 (0.06)							
	0	0	3 (0.06)†	0	3 (0.03)	0							
<b>Diaphragmatic Hernias</b>													
Hiatus Hernia	3 (0.28)	1 (0.11)†	35 (0.66)†	31 (0.76)	67 (0.65)	22 (1.22)							
	3 (0.28)	1 (0.11)	35 (0.66)	31 (0.76)	67 (0.65)	22 (1.22)							

<sup>1</sup> Sponsor's Table 32. Treatment-Emergent Adverse Events Experienced by  $\geq 1$  Subject per 100 PM of Exposure in Any Treatment Group in All Phase 3 Studies, from 5.3.5.3. Integrated Summary of Safety, pp.121-122.

<sup>2</sup> Data in this table does not include LTS safety findings from the 4-Month Safety Update.

\* Indicates a statistically significant difference versus placebo ( $p \leq 0.05$ ).

† Indicates a statistically significant difference versus lansoprazole 30 mg QD ( $p \leq 0.05$ ).

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In Phase 3 HEE studies, the most frequently occurring AE in any treatment group was diarrhea. No statistically significant differences were demonstrated between treatment groups.

For Phase 3 MHEE studies, the most frequently occurring AEs in Dexlansoprazole and lansoprazole were URIs and diarrhea. A dose-related incidence trend was seen for diarrhea where incidence rate increased (0.78, 1.21, and 1.46/100 PM) with increasing dose of Dexlansoprazole (30-mg, 60-mg, and 90-mg, respectively). Placebo subjects experienced more dyspepsia, gastritis, nausea and vomiting, esophageal ulcers and perforation, and gastric ulcers and perforation.

During the Phase 3 GERD studies, the most frequently reported AEs were similar to those listed above for all Phase 3 studies. It was noted, however, that URI adverse events were most prevalent and statistically significant in the 90mg Dexlansoprazole treatment group, when compared to the other doses of Dexlansoprazole and placebo.

The LTS study reported similar common AEs as those listed above for all Phase 3 studies. The most frequently reported adverse event was URIs, with the highest proportion per treatment group (11.7-14.4%). [See Table 7.4.1.2.] There was an additional frequently reported HLT of Musculoskeletal and Connective Tissue Signs and Symptoms (3.7-7.2%), which included AEs such as back pain, flank pain, musculoskeletal pain, neck pain, and pain in extremity.

**Table 7.4.1.2. Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects in Any Treatment Group in the Long-Term Safety Study<sup>1</sup>**

MedDRA High Level Term Preferred Term	Dexlansoprazole Treatment Group n (%)				
	60 mg QD (N=153)	90 mg QD		All Subjects	
		ISS	Update	ISS	Update
		90 mg QD (N=160)	90 mg QD (N=438)	Total (N=313)	Total (N=591)
Average Patient Days of Exposure	285.8	267.1	225.8	276.2	241.3
<b>Total Subjects With ≥1 Adverse Event</b>	<b>109 (71.2)</b>	<b>105 (65.6)</b>	<b>245 (55.9)*</b>	<b>214 (68.4)</b>	<b>354 (59.9)</b>
<b>Upper Respiratory Tract Infections</b>	<b>22 (14.4)</b>	<b>23 (14.4)</b>	<b>47 (10.7)</b>	<b>45 (14.4)</b>	<b>69 (11.7)</b>
Laryngitis	1 (0.7)	0	2 (0.5)	1 (0.3)	3 (0.5)
Nasopharyngitis	6 (3.9)	5 (3.1)	12 (2.7)	11 (3.5)	18 (3.0)
Pharyngitis	0	0	1 (0.2)	0	1 (0.2)
Sinusitis	5 (3.3)	9 (5.6)	16 (3.7)	14 (4.5)	21 (3.6)
Tonsillitis	1 (0.7)	0	0	1 (0.3)	1 (0.2)
Upper Respiratory Tract Infection	12 (7.8)	11 (6.9)	18 (4.1)	23 (7.3)	30 (5.1)
<b>Gastrointestinal and Abdominal Pains (Excl Oral and Throat)</b>	<b>10 (6.5)</b>	<b>20 (12.5)</b>	<b>42 (9.6)</b>	<b>30 (9.6)</b>	<b>52 (8.8)</b>
Abdominal Pain	2 (1.3)	7 (4.4)	18 (4.1)	9 (2.9)	20 (3.4)
Abdominal Pain Lower	3 (2.0)	4 (2.5)	8 (1.8)	7 (2.2)	11 (1.9)
Abdominal Pain Upper	5 (3.3)	7 (4.4)	11 (2.5)	12 (3.8)	16 (2.7)
Abdominal Tenderness	0	2 (1.3)	7 (1.6)	2 (0.6)	7 (1.2)
Gastrointestinal Pain	1 (0.7)	0	0	1 (0.3)	1 (0.2)

MedDRA High Level Term Preferred Term	Dexlansoprazole Treatment Group n (%)				
	60 mg QD (N=153)	90 mg QD		All Subjects	
		ISS	Update	ISS	Update
		90 mg QD (N=160)	90 mg QD (N=438)	Total (N=313)	Total (N=591)
<b>Diarrhoea (Excl Infective)</b>	<b>18 (11.8)</b>	<b>13 (8.1)</b>	<b>32 (7.3)</b>	<b>31 (9.9)</b>	<b>50 (8.5)</b>
Diarrhoea	18 (11.8)	13 (8.1)	32 (7.3)	31 (9.9)	50 (8.5)
<b>Nausea and Vomiting Symptoms</b>	<b>13 (8.5)</b>	<b>17 (10.6)</b>	<b>32 (7.3)</b>	<b>30 (9.6)</b>	<b>45 (7.6)</b>
Nausea	10 (6.5)	13 (8.1)	24 (5.5)	23 (7.3)	34 (5.8)
Regurgitation	0	0	1 (0.2)	0	1 (0.2)
Retching	0	1 (0.6)	1 (0.2)	1 (0.3)	1 (0.2)
Vomiting	4 (2.6)	6 (3.8)	9 (2.1)	10 (3.2)	13 (2.2)
<b>Headaches NEC</b>	<b>11 (7.2)</b>	<b>15 (9.4)</b>	<b>25 (5.7)</b>	<b>26 (8.3)</b>	<b>36 (6.1)</b>
Headache	10 (6.5)	13 (8.1)	22 (5.0)	23 (7.3)	32 (5.4)
Sinus Headache	0	2 (1.3)	2 (0.5)	2 (0.6)	2 (0.3)
Tension Headache	1 (0.7)	0	1 (0.2)	1 (0.3)	2 (0.3)
<b>Musculoskeletal and Connective Tissue Signs and Symptoms NEC</b>	<b>11 (7.2)</b>	<b>7 (4.4)</b>	<b>16 (3.7)</b>	<b>18 (5.8)</b>	<b>27 (4.6)</b>
Back Pain	5 (3.3)	4 (2.5)	8 (1.8)	9 (2.9)	13 (2.2)
Flank Pain	0	1 (0.6)	3 (0.7)	1 (0.3)	3 (0.5)
Musculoskeletal Pain	1 (0.7)	0	3 (0.7)	1 (0.3)	4 (0.7)
Neck Pain	3 (2.0)	0	1 (0.2)	3 (1.0)	4 (0.7)
Pain In Extremity	3 (2.0)	2 (1.3)	2 (0.5)	5 (1.6)	5 (0.8)
<b>Flatulence, Bloating and Distension</b>	<b>6 (3.9)</b>	<b>11 (6.9)</b>	<b>21 (4.8)</b>	<b>17 (5.4)</b>	<b>27 (4.6)</b>
Abdominal Distension	4 (2.6)	10 (6.3)	17 (3.9)	14 (4.5)	21 (3.6)
Flatulence	2 (1.3)	3 (1.9)	6 (1.4)	5 (1.6)	8 (1.4)

<sup>1</sup> Sponsor's Table 9. Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects in Any Treatment Group in the Long-Term Safety Study from 5.3.5.4. 4-Month Safety Update, pp. 39-40.  
 \* Indicates a statistically significant difference versus dexlansoprazole 60 mg (p≤0.05).

**Reviewer's Comments:**

*The overall common AEs are similar to those already noted on currently marketed PPIs. It is expected that subjects in the placebo treatment group of the MHEE studies experience symptoms and complications of EE as they are not receiving active drug therapy. It is curious, however, that within the GERD studies, there lays an unexplained imbalance of URIs between the 90mg and other two doses of Dexlansoprazole. Lastly, within the LTS study, new and unexpected frequently reported adverse events in Musculoskeletal and Connective Tissue Signs and Symptoms (which do not include asthenia) may warrant further study on the long-term effects of Dexlansoprazole on the musculoskeletal system.*

7.4.2 Laboratory Findings

7.4.2.1. Hematology

For the Phase 3 studies, mean changes from baseline for the majority of hematology parameters were small and did not demonstrate statistical significance, except for changes in hemoglobin, hematocrit, and platelet count which showed significant difference. In the MHEE studies, mean

decreases from baseline were small and demonstrated a dose-related trend for hemoglobin, hematocrit, and platelet count. These values, however, remained within normal limits. In GERD studies, a small mean decrease in hemoglobin was significant in Dex treatment groups compared to placebo. In HEE studies, no statistical differences were shown between Dexlansoprazole and lansoprazole treatment groups. The percentage of subjects with PCI values ranged from 0-2% across studies, except for MHEE and LTS studies. A higher proportion of Dexlansoprazole subjects (6-9%) had low hemoglobin compared to placebo subjects (2%) in MHEE studies (see table), while in the LTS 6% of subjects had low hemoglobin.

**Table 90. Summary of Subjects With PCI Hemoglobin Parameters by Visit in the Phase 3 Maintenance of Healed EE Studies**

Hematology Parameter Criteria Timepoint	Treatment Group: n/N (%)				
	Placebo (N=287) (Avg PD=53)	Dexlansoprazole MR			Total (N=609) (Avg PD=138)
		30 mg QD (N=140) (Avg PD=137)	60 mg QD (N=317) (Avg PD=140)	90 mg QD (N=152) (Avg PD=135)	
<b>Hemoglobin</b>					
Low					
Month 1	2/233 (<1)	4/125 (3)	7/296 (2)	6/141(4)	17/562 (3)
Month 3	2/58 (3)	3/105 (3)	3/247 (3)	3/113 (3)	14/465 (3)
Month 6	1/40 (3)	1/24 (1)	2/204 (4)	10/94 (11)	19/382 (5)
Any Visit	5/235 (2)	7/127 (6)	17/299 (6)*	13/142 (9)*	37/568 (7)

Studies included: T-EE04-086 and T-EE04-087, and T-EE05-135.

Avg PD=average patient-days.

\* Statistically significant versus placebo (p<0.05).

5.3.5.3. Integrated Summary of Safety p.237

Although, due to the high discontinuation rate in the MHEE placebo population, sampling bias may be the reason for the statistical difference of low hemoglobin in Dexlansoprazole treatment groups compared to placebo, these results initiated a special focus on anemia as an adverse event for the overall Dexlansoprazole treatment population that is discussed above, in Section 7.3.4. In Phase 1 studies, 0 to <1% of subjects had potential clinically important (PCI) values for the majority of parameters, and none associated with adverse events. Fifteen of 19 subjects in the warfarin drug interaction study demonstrated the expected PT elevation.

#### 7.4.2.2. Chemistry

For Phase 3 studies, mean changes from baseline in chemistry parameters were small. Subjects with PCI values ranged 0-3%. Subjects with elevated liver enzymes ranged from 0-2%, and included elevations of  $\geq 3x$  ULN or  $\geq 5x$  ULN for ALT or AST and  $\geq 3x$  ULN for ALT and AST. No subject had concurrent elevations of hepatic enzymes and total bilirubin. No subject had elevations that met the Hy's law criteria for drug-induced liver injury. No subject had hepatic enzymes elevations  $\geq 10$  ULN. In Phase 1 studies, 0-2% of subjects had PCI values.

#### 7.4.2.3. Urinalysis

For Phase 3 studies, mean changes from baseline for urinalysis parameters were not clinically meaningful. Subjects with PCI values were <3%. For Phase 1, one multi-dose study subject had a high pH PCI results

### 7.4.3 Vital Signs

For Phase 3 studies, no clinically meaningful changes were seen in vital sign parameters. For MHEE and GERD studies, sporadic statistically significant differences were demonstrated for SBP, DBP, pulse, and weight; however, there were no meaningful trends. Subjects with PCI values ranged from 0-2% and none had associated adverse events. In Phase 1 studies, 2% of subjects in multiple-dose studies had low SBP or DBP, and none had associated adverse events.

### 7.4.4 Electrocardiograms (ECGs)

ECGs were performed on a subset of subjects (n=535), during the Phase 3 GERD study T-GD05-137, and evaluated by a blinded cardiologist. ECGs were not coordinated with food intake or study drug administration, and no PK samples were collected. Cardiologist evaluated all subjects who had increases in QTcF and/or QTcB intervals to reveal no clinical concerns.

**Table 125. Summary of PCI QT/QTc Interval Values in the Symptomatic GERD Study T-GD05-137**

Variable Criteria	Placebo (N=317) n/N (%)	Dexlansoprazole IR		Total (N=630) n/N (%)
		30 mg QD (N=315) n/N (%)	60 mg QD (N=315) n/N (%)	
<b>QT/QTc Interval (msec)</b>				
≥450	6/179 (3)	4/182 (2)	6/174 (3)	10/356 (3)
Increase ≥30	10/179 (6)	20/182 (11)	14/174 (8)	34/356 (10)
≥450 or increase ≥30	15/179 (8)	22/182 (12)	18/174 (10)	40/356 (11)
≥450 and increase ≥30	1/179 (<1)	2/182 (1)	2/174 (1)	4/356 (1)
<b>QTcF Interval (msec)</b>				
≥450	2/179 (1)	5/182 (3)	3/174 (2)	8/356 (2)
Increase ≥30	10/179 (6)	11/182 (6)	9/174 (5)	20/356 (6)
≥450 or increase ≥30	11/179 (6)	12/182 (7)	11/174 (6)	23/356 (6)
≥450 and increase ≥30	1/179 (<1)	4/182 (2)	1/174 (<1)	5/356 (1)
<b>QTcB Interval (msec)</b>				
≥450	3/179 (2)	11/182 (6)	8/174 (5)	19/356 (5)
Increase ≥30	12/179 (7)	15/182 (8)	10/174 (6)	25/356 (7)
≥450 or increase ≥30	14/179 (8)	19/182 (10)	16/174 (9)	35/356 (10)
≥450 and increase ≥30	1/179 (<1)	7/182 (4)	2/174 (1)	9/356 (3)

Study included: T-GD05-137.

Sponsor's Table, from 5.3.5.3.Integrated Summary of Safety p.280

The Phase 1 Thorough ECG study (T-P104-092) failed to demonstrate that Dexlansoprazole prolonged the QT/QTc interval, at 90mg and 300mg doses, when compared to placebo. Other Phase 1 studies saw no clinically important changes in ECGs.

### 7.4.5 Special Safety Studies

#### 7.4.5.1. Serum Gastrin

As serum gastrin increases are an expected physiological response to the action of PPIs, these levels were followed in clinical studies. Serum gastrin was collected from both fasted and fed subjects. In Phase 3 studies, all Dex treatment groups demonstrated increases in serum gastrin level, where subjects of baseline values <100pg/ml, had on-treatment values <300pg/ml. In HEE studies, statistically significant increases were seen for each Dex treatment group compared to lansoprazole, and when compared to each other. In MHEE and GERD studies, mean increases in

serum gastrin levels were statistically significant when Dex treatment groups were compared to placebo, but not when Dex treatment groups were compared to each other. Phase 3 studies of longer duration, MHEE (6 mo.) and LTS (12 mo.), illustrated that serum gastrin levels in Dexlansoprazole subjects increase steadily over the first 3 months of treatment and plateau afterwards. Those patients who received Dexlansoprazole or lansoprazole in the HEE study, to later rollover to placebo in the MHEE study, all had their serum gastrin levels return to normal within the first month on placebo.

In Phase 1 studies, mean serum gastrin was significantly increased from baseline for subjects on 90mg or 120mg Dexlansoprazole or on 30mg lansoprazole. Serum gastrin returned to baseline seven days after last dose of study drug.

#### 7.4.5.2. Gastric Biopsies

Gastric biopsies were performed during endoscopy at the final visit for MHEE and LTS studies, with baseline biopsies performed in prior studies. Unfortunately, this method left no final biopsy comparison for the lansoprazole treatment group. From Phase 3 MHEE study, no clinically important differences were seen between the Dexlansoprazole treatment group and placebo. For the Phase 3 LTS study, chronic gastritis was the most common tissue abnormality in the antral (30.8%) and/or fundic (35.9%) region for subjects in the 60mg and 90mg Dexlansoprazole treatment groups, respectively. Although 0.8% of subjects had intestinal metaplasia at the final visit, no subjects had dysplasia or adenocarcinoma and there were no reports of ECL hyperplasia.

#### 7.4.5.3. Barrett's Esophagus

**Subjects found with Barrett's esophagus during Phase 3 clinical studies** were explained as 1) not being excluded from enrollment due to a lag in processing of screening biopsy results, 2) being discovered once PPI treatment reduced surrounding tissue inflammation, and 3) being discovered upon PPI treatment and successful healing of adjacent esophageal erosions. The majority of these subjects were enrolled in the HEE studies, **and the Barrett's esophagus resulted in premature discontinuation with or without adverse event reporting.** There were 109 subjects **suspected of Barrett's esophagus in the HEE studies:** 26 of the 28 recognized during screening were discontinued, while 2 of the 28 completed studies on 90mg Dexlansoprazole; 18 of the 81 recognized during treatment discontinued, while 62 completed studies on 60mg or 90mg Dexlansoprazole or on 30mg lansoprazole. In MHEE studies, 24 subjects were suspected with **Barrett's esophagus:** 13 of the 15 recognized during screening or treatment of the HEE study were discontinued, while 2 of the 15 completed studies on 60mg or 90mg Dexlansoprazole; 6 of the 9 recognized during treatment of the MHEE study discontinued, while 3 completed studies on 30mg or 60mg or 90mg Dexlansoprazole.

#### 7.4.5.4. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

A focused review on ability to drive or operate machinery or impairment of mental ability was performed in Phase 3 studies, as 4 motor vehicle accidents (MVA) were reported. Three MVAs occurred with subjects receiving Dexlansoprazole and 1 MVA with a subject on lansoprazole. The incidence for adverse events reported under MedDRA HLT of Disturbances in Consciousness NEC (Lethargy, Loss Of Consciousness, Somnolence, Syncope, and Syncope Vasovagal) were similar for Dexlansoprazole and lansoprazole treatment groups; where there was a zero incidence in placebo subjects, a 0 to 0.1/100PM incidence in Dexlansoprazole

subjects, and a 0.11/100PM incidence in lansoprazole. The incidence of AEs reported under MedDRA HLT of Neurological Signs and Symptoms NEC (Dizziness) was highest in the lansoprazole treatment group (0.61/100PM) versus placebo (0.28/100PM) and Dexlansoprazole groups (0.29-0.32/100PM). It was concluded that Dexlansoprazole does not effect ability to drive or operate machinery.

#### 7.4.6 Immunogenicity

There was no focused review on the ability of Dexlansoprazole to elicit an adverse immune response. However, there were no reports of anaphylaxis/anaphylactoid reactions as adverse events associated with Dexlansoprazole.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

In all Phase 3 studies, there were few instances of dose-dependent increases in AE incidence for **Dexlansoprazole**. **Across all studies, there was an increasing incidence of SAE's with increasing dose:** 0.43, 0.49, and 0.48 subjects per 100PM in the 30mg, 60mg, and 90mg Dexlansoprazole treatment groups, respectively. In one GERD study (T-GD04-082), the risk of upper respiratory tract infections was statistically significant for 90mg Dexlansoprazole (8%) when compared to 60mg dexlansoprazole (4%) and the placebo groups (1%). In the MHEE studies, increasing incidence of Diarrhoea (Excl Infective) occurred with increasing dose; however, there were no statistically significant difference between treatment groups.

##### 7.5.1.1 Food Effect

In Phase 3 studies, all study drug was administered before breakfast according to the lansoprazole labeling in order to maintain blinding and consistency. Therefore, no assessment of food effect could be performed. In Phase 1 PK/PD studies, no difference was seen between the fasted or fed regimens with regard to adverse event reporting.

#### 7.5.2 Time Dependency for Adverse Events

See section 7.3.5.1.

#### 7.5.3 Drug-Demographic Interactions

##### 7.5.3.1 Age

Overall, there was no interaction demonstrated by age when treatment-emergent AEs were analyzed between treatment groups. Increased incidence of diarrhea with increasing age was shown in HEE trials within the dexlansoprazole 90mg and lansoprazole 30mg treatment groups. No clinically important changes in laboratory values were observed by age. The sponsor cites no evidence to support dose adjustment in the elderly.

#### 7.5.3.2 Gender

Overall, there was no interaction demonstrated by gender when treatment-emergent AEs were analyzed by treatment groups. Increased incidence of AEs was shown among females in HEE trials. No clinically important changes in laboratory values were observed by gender. The sponsor cites no evidence to support dose adjustment based on gender.

#### 7.5.3.3 Race/Ethnicity

There was no interaction demonstrated by race/ethnicity when treatment-emergent AEs were analyzed by treatment groups. No clinically important changes in laboratory values were observed by race/ethnicity. The sponsor cites no evidence to support dose adjustment based on race/ethnicity.

#### 7.5.3.4 Body Mass Index

Overall, there was no interaction demonstrated by BMI when treatment-emergent AEs were analyzed by treatment group. Increased incidence of AEs with increasing BMI was shown in GERD trials within the dexlansoprazole 90mg treatment group. No clinically important changes in laboratory values were observed by BMI. The sponsor cites no evidence to support dose adjustment based on BMI.

#### 7.5.3.5 Alcohol Use

There were statistically significant differences demonstrated by alcohol use status when treatment-emergent AEs were analyzed by treatment group. By study indication, alcohol users were more likely to report AEs in HEE and GERD trials. In HEE, a 10% statistically significantly higher risk of AE was reported in the 90mg Dex group compared to placebo. In GERD, a similarly significant 15% increased risk was shown between the same treatment groups. No clinically important changes in laboratory values were observed by alcohol use status. In MHEE, the overall incidence of AEs was not statistically significantly different between alcohol users and non-users by treatment group.

#### 7.5.3.6 Tobacco Use

There was no interaction demonstrated by tobacco use status when treatment-emergent AEs were analyzed by treatment group. The overall AE incidence rate was not statistically significantly different between subjects between tobacco users and non-users by treatment group. No clinically important changes in laboratory values were observed by tobacco use status.

#### 7.5.3.7 Country

The sponsor conducted Phase 3 trials at both sites in the United States (approximately 200 sites) and outside the United States (approximately 200 sites). Those ex-US countries and the estimated numbers of sites in those countries are as follows: Australia (13), Bulgaria (18), Canada (24), Czech Republic (10), Estonia (2), Finland (5), Hungary (10), India (22), Israel (10), Latvia (10), Lithuania (7), New Zealand (7), Poland (10), Russia (20), Slovakia (7), South Africa (13), United Kingdom (19), Ukraine (12).

There exists a statistically significant difference in AE incidence rates between US and non-US study sites when AEs were analyzed by treatment group. Adverse event incidence rates by study site and treatment groups are shown in tables below for HEE and MHEE studies. All GERD studies were conducted at US sites.

**Table 7.5.3.7.1 Overall Risk for Adverse Events by Country in HEE Studies<sup>1</sup>**

MedDRA High Level Term	Treatment Group: n (%)					
	Dexlansoprazole				Lansoprazole	
	60 mg (N=1374)		90 mg (N=1355)		30 mg QD (N=1363)	
	Country					
	US (n=1001)	Non-US (n=373)	US (n=972)	Non-US (n=383)	US (n=987)	Non-US (n=376)
Total Subjects With ≥1 Adverse Event*†‡	329 (32.9)	89 (23.9)	298 (30.7)	83 (21.7)	302 (30.6)	77 (20.5)

<sup>1</sup> Sponsor's Table 182 from 5.3.5.3. Integrated Summary of Safety, p. 409; studies included: T-EE04-084 and T-EE04-085.  
 \* Statistically significant within treatment comparison between strata in the dexlansoprazole 60-mg QD group (p≤0.05).  
 † Statistically significant within treatment comparison between strata in the dexlansoprazole 90-mg QD group (p≤0.05).  
 ‡ Statistically significant within treatment comparison between strata in the lansoprazole 30-mg QD group (p≤0.05).

**Table 7.5.3.7.2 Overall Incidence Rates for Adverse Events by Country in MHEE Studies<sup>1</sup>**

MedDRA High Level Term	Treatment Group: n (rate per 100 PM)							
	Placebo		Dexlansoprazole					
	(N=287) (Avg PM=1.8)		30 mg QD (N=140) (Avg PM=4.6)		60 mg QD (N=317) (Avg PM=4.7)		90 mg QD (N=152) (Avg PM=4.5)	
	Country							
	US (n=272) (PM=1.7)	Ex US (n=15) (PM=2.4)	US (n=123) (PM=4.5)	Ex US (n=17) (PM=4.6)	US (n=295) (PM=4.6)	Ex US (n=22) (PM=5.8)	US (n=152) (PM=4.5)	Ex US (n=0) (PM=0)
Total Subjects With ≥1 Adverse Event*†‡	75 (15.94)	5 (13.93)	61 (10.92)	5 (6.33)	156 (11.52)	6 (4.69)	66 (9.65)	0
Dyspeptic Signs and Symptoms‡	7 (1.49)	1 (2.79)	3 (0.54)	0	5 (0.37)	1 (0.78)	0	0

<sup>1</sup> Sponsor's Table 183 from 5.3.5.3. Integrated Summary of Safety, p. 412; Studies included: T-EE04-086, T-EE04-087, and T-EE05-135.  
 \* Statistically significant within treatment comparison between strata in the dexlansoprazole 60-mg QD group (p≤0.05).  
 † Statistically significant pairwise comparison between the dexlansoprazole 30-mg QD and placebo groups adjusting for country (p≤0.05).  
 ‡ Statistically significant pairwise comparison between the dexlansoprazole 60-mg QD and placebo groups adjusting for country (p≤0.05).

There were no clinically important changes in laboratory values were observed by country.

**Reviewer's comments:**

*In both HEE and MHEE trials, there were consistently less incidence of AEs in non-US vs. US sites. This difference may reflect reporting differences, the patient culture, or the nation's standard of care. Consideration of this reporting difference may warrant that AEs listed in the label be restricted to only those events that occurred in the US.*

## 7.5.4 Drug-Disease Interactions

### 7.5.4.1 Hepatic Impairment

One Phase 1 study (T-P105-115) was performed to assess the pharmacokinetics of a single dose of 60mg Dexlansoprazole in hepatic impaired subjects. Subjects with moderate hepatic impairment were enrolled and subjects with normal hepatic function were matched to them. Safety analyses, including adverse events, laboratory values, physical examinations, vital signs, and ECGs, did not suggest any safety concerns for this population under the prescribed single-dose regimen. The sponsor states that no dosage adjustment for doses up to 60 mg is necessary for patients with mild or moderate hepatic impairment (Child Pugh Class A or B).

### 7.5.4.2 Renal Impairment

No studies were performed to evaluate the pharmacokinetics of Dexlansoprazole in renal impaired subjects because Dexlansoprazole is completely metabolized in the liver to inactive metabolites. The sponsor states that no dose adjustment is needed in renal impairment patients.

### 7.5.4.3 Specific Comorbid Conditions

There were no clinically meaningful differences in adverse events when evaluated by study indication, other than those already anticipated from comorbid conditions. In GERD trials, subjects with a history of allergy reported more adverse events. No clinically important changes in laboratory values were observed by comorbid conditions.

## 7.5.5 Drug-Drug Interactions

For Phase 3 controlled studies, no clinically important adverse events occurred during concomitant use of Dexlansoprazole and medications such as calcium, acetylsalicylic acid, anti-hypertensives, statins, and anticoagulants. Nonetheless, concomitant use with NSAIDs revealed a higher AE incidence. No clinically important mean changes from baseline were seen for laboratory values with use of any of these concomitant medications.

Phase 1 studies demonstrate that no dose adjustment is needed when Dexlansoprazole is used in conjunction with phenytoin, theophylline, diazepam or warfarin. Further review of drug-drug interaction is provided in the Clinical Pharmacology review of this application by Dr. J. P. Bai.

## 7.6 Additional Safety Explorations

### 7.6.1. Human Carcinogenicity

There was no formal assessment of human carcinogenicity in Dexlansoprazole studies as the study durations were 1 month to 1 year. Information about gastric polyps is presented in Section 7.3.4.4, and for precancerous tissue changes in the esophagus see Section 7.4.5., under Gastric Biopsies and Barrett's Esophagus.

### 7.6.2. Human Reproduction and Pregnancy Data

There were thirteen (13) subjects who, testing negative during the screening period, became pregnant upon the start of Phase 3 studies. Ten had been randomized to receive dexlansoprazole. From the ten, 6 elected to have abortions, 1 experienced a spontaneous abortion, and 3 live births resulted. Once a subject became pregnant, she was discontinued and followed to resolution (abortion or live birth). The table below lists the 4 subjects who decided not to electively abort.

**Table 7.6.2.1 Results of Pregnancies Continued After Exposure to Dexlansoprazole.**

Patient No./ Age/Parity*/ Sig Med Risk Factors/ Study No.	Pregnancy test results	Exposure to Dex	Estimated gestational age at study discontinuation	Disposition
# 9172016 34 y.o. G5P130 GestDM, HTN	Negative screening, positive on day 9	60mg x 8 days	19d	D/C from study on day 12; live birth, healthy infant
# 19463022 26 y.o. G3P011 T-GD05-137	Negative screening, positive on day 12	30mg x 12 days	21d	D/C from study on day 12; live birth, healthy infant
# 9172128 44 y.o. G3P020 Brain calcif on Tegretol, T-EE04-084 T-EE05-135	Negative on day 37, positive on day 96	60mg x 28 days 30mg x 68 days	18d	D/C from study on day 96; spontaneous ab on day 102, considered unrelated to study drug
# 18128160 28 y.o. G3P2, PIHtn T-EE04-084 T-EE05-135	Negative on day 30, positive on day 78	60mg x 28 days 30mg x 50 days	20d	D/C from study on day 78; live birth, healthy infant

\*Parity = # of times gravid, # of premature births, # of abortions (elective or spontaneous), # of live births

**Reviewer's comments:**

*The very few pregnant women (n=4) observed to term, post exposure to dexlansoprazole, suggest minimal drug effect on the fetus. However, without a clinical trial the evidence is uncertain. At*

*this time, the best evidence of Dex drug effect on reproduction comes from animal data. See Pharmacology/Toxicology review by Dr. Zhang.*

### 7.6.3 Pediatrics and Effect on Growth

There were no studies to evaluate pediatrics and effect on growth. The Sponsor has requested a deferral of pediatric studies required under the Pediatric Research Equity Act (PREA) for patients aged 1 month to 17 years and a waiver for patients aged 0 to 1 month.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose was reported in 17 subjects in Phase 3 studies. The majority of subjects inadvertently took an extra dose of study drug for 1 to 30 days, while 1 subject took an extra dose because she had missed the prior dose. No adverse events were reported with these events. The drug abuse potential, physiological or psychological dependency, was not assessed; nor were there studies to evaluate withdrawal and rebound effects.

## 7.7 Additional Submissions

For ease of discussion, all additional submissions have been incorporated in the body of the safety review. Please note, however, that safety results of the LTS study were provided in the 4-Month Safety Update. The final report of long-term safety study will be available in the 1<sup>st</sup> quarter of 2009.

## 8 Postmarketing Experience

Dexlansoprazole has not been approved or marketed in any country. There exists no postmarketing surveillance data.

Its racemic parent, lansoprazole, has been marketed in 93 countries with an estimated patient exposure greater than 432 million persons since its approval in 1995. AERS postmarketing surveillance reports have captured 239 deaths where lansoprazole has been the suspected agent during the same time period. Therefore, the mortality rate is estimated at 0.0046 (239/432 million/12 years x 100,000) per 100,000 population exposed to lansoprazole. By this data, death caused by lansoprazole is a very rare event. Discussed below are additional safety evaluations of adverse events of interest in the lansoprazole postmarketing surveillance database and clinical trial database (not including Phase 1 or Special Design crossover trials). The adverse events of interest are cardiovascular events, hip fracture/calcium homeostasis, gastric polyps, upper and lower respiratory tract infections, cholestatic disorders/abnormal liver enzymes/pancreatitis, *C. difficile* associated disease and anemia. These AEs are similar to those explored for dexlansoprazole in the above Section 7.3.4 Significant Adverse Events. Their estimated incidence rates, in regards to the postmarketing population exposure, make them very rare events for lansoprazole.

## **8.1 Cardiovascular Risk**

The sponsor reviewed their randomized controlled clinical trials (RCTs) database to evaluate preferred terms relevant to serious cardiovascular adverse events. Subjects who received lansoprazole had a 0.6% risk of serious cardiovascular events. This was similar to the study comparators. Of those subjects having a qualified CV event of interest, 89% subjects had at least 1 identifiable baseline risk factors.

## **8.2 Hip Fracture and Calcium Homeostasis**

The sponsor reviewed their clinical trials database and postmarketing surveillance database (cutoff January 31, 2008) for preferred terms relevant to AEs of fracture and calcium metabolism disorders. The clinical trials database also provided mean serum calcium and phosphorus levels.

Postmarketing data revealed 59 cases with 63 qualified adverse events, 22 of which were deemed serious. Fifteen were bone fractures: 6 located in the hip, 3 in the spine. All hip fracture cases were female, except for 1 male who had a history of hip replacement on the same side as fracture. There was a noted increased postmarketing reporting rate during the 6 months following the article by Yang et al. (see References), who brought attention to this issue. Of the remaining 48 calcium metabolism disorders reported, the majority (38%) were osteoporosis.

RCTs demonstrated that study subjects who received lansoprazole had a 0.03% risk of bone fracture or calcium metabolism disorder. This risk was not dissimilar to the risk of those in the comparator or placebo treatment groups. The incidence rate of fracture or calcium metabolism disorder among subjects in the lansoprazole treatment group was 2.73/100PY exposure, compared to 2.56/100PY and 3.19/100PY exposure of comparator and placebo treatment groups. Subjects in the lansoprazole treatment group reporting bone fracture, other than hip fracture, demonstrated similar risk profiles as when both bone fracture and calcium metabolism disorder were analyzed. There was no occurrence of hip fracture among subjects on lansoprazole in any of the RCTs, and 1 occurrence of hip fracture in a comparator treatment group. There was one report of calcium metabolism disorder, occurring in the lansoprazole treatment group: a 75 y.o female with hypocalcemia post 1 day on lansoprazole. RCTs showed no sizeable change from baseline and no dose-related trends for mean calcium and phosphorous levels.

Among uncontrolled lansoprazole-only trials, the risk of bone fracture or calcium metabolism disorders was 4.8%, with an incidence rate of 2.48 per 100 patient-months exposure. The risk of hip fractures was 0.5%, bone fractures (2.9%), and calcium

metabolism disorders (1.3%). No sizable change from baseline and no dose-related trends were seen for mean calcium and phosphorous levels.

### **8.3 Hepatic Enzyme Abnormalities/Cholestatic Disorders/Pancreatitis**

Randomized clinical trials revealed that the risk and incidence rate of hepatic enzyme abnormalities/cholestatic disorders/pancreatitis among subjects on lansoprazole were not dissimilar to that of those placebo and comparators. Only one serious case of abnormal liver enzymes was reported. In postmarketing surveillance 148, 245, and 45 serious cases of cholestatic disorders, abnormal liver enzymes and pancreatitis, respectively, were identified. No safety signal was observed.

### **8.4 Gastric Polyps**

Randomized clinical trials revealed that there is a low risk of gastric polyps with lansoprazole, however, gastric polyps observed during study protocol endoscopy examinations were not included as adverse events. Twelve serious and 54 nonserious cases were found. No safety signal was observed.

### **8.5 Upper Respiratory Tract Infections**

Randomized clinical trials revealed that study participants who received lansoprazole had a 9.63% risk of URTIs, with 1 out of the 1,040 URTIs reported as serious. The incidence rate among subjects in the lansoprazole treatment groups was 6.86 per 100PM of exposure. The risk and incidence rate of URTIs among subjects on placebo and comparators were not dissimilar to that of those lansoprazole. Uncontrolled lansoprazole-only trials yielded an incidence rate of 1.20 per 100PM exposure, while *H. pylori* eradication trials yielded a risk of 8.18% in subjects on lansoprazole alone. Postmarketing surveillance found 170 qualified cases, with 10 of the 170 reported as serious.

### **8.6 Lower Respiratory Tract Infections**

Randomized clinical trials revealed subjects who received lansoprazole had a 1.03% risk of LRTIs, including pneumonia. The incidence rate among subjects in the lansoprazole treatment groups was 0.73 per 100PM of exposure. The risk and incidence rate of LRTIs among subjects on placebo and comparators were not dissimilar to that of those lansoprazole. Uncontrolled lansoprazole-only trials yielded an incidence rate of 0.32 per 100PM exposure, with half the events reported as serious. The *H. pylori* eradication trials yielded a risk of 0.61% in subjects on lansoprazole alone. Postmarketing surveillance found 124 qualified events in 122 cases. The majority (77%) was reported as serious and most frequently represent interstitial lung disease (58%) and pneumonia (20%). The estimated risk of LRTIs in the postmarketing population (455 million) is less than 1 in 3,500,000 persons.

## 8.7 Anemia

Randomized clinical trials revealed a very low reporting frequency of anemia serious adverse events. Underreporting is likely due to the fact that anemia is already a labeled adverse event of lansoprazole. There were 146 serious cases of anemia reported. No new safety signal was observed.

## 8.8 Clostridium difficile-associated Diseases

Among randomized clinical trials and uncontrolled lansoprazole-only trials, each had 1 report of *C. difficile*-associated disease (CDAD). Therefore, the risk and incidence rate of CDAD was <0.01% and 0.01 per 100PM exposure, respectively. For the RCTs, there were no reported CDAD among placebo and comparators. No CDAD were reported in the *H. pylori* eradication trials. The postmarketing surveillance yielded 269 cases matching MedDRA Preferred Terms. Further selection for qualified events identified 28 AEs reporting pseudomembranous colitis, plus associated *C. difficile* infection, or *C. difficile* positive test; or reporting diarrhea with associated *C. difficile* positive test results. The majority (86%) of these qualified events occurred within the first 8 days of concomitant antibiotic use. The estimated risk of CDADs in the postmarketing population (455 million) is 1 in 16,250,000 persons.

## 9 Appendices

List of Abbreviations and Definitions of Terms

Table 7.1.1.2. Listing of Phase 3 Clinical Studies

Table 7.1.1.3. Brief Descriptions of Phase 1 Studies Conducted with Dexlansoprazole<sup>1</sup>

Table 7.3.1.2. Phase 3 Clinical Studies Deaths Listing

Table 7.3.2.5. Phase 3 Nonfatal Serious Adverse Event Possibly Drug Related in Phase 3 Trials

Table 7.3.2.6. Nonfatal Serious Adverse Event Listing in Phase 3 HEE Studies

Table 7.3.2.7. Nonfatal Serious Adverse Event Listing in Phase 3 MHEE Studies

Table 7.3.2.8. Nonfatal Serious Adverse Event Listing in Phase 3 GERD Studies

Table 7.3.2.9. Nonfatal Serious Adverse Event Listing in Phase 3 LTS Study

Table 7.3.4.1.4. 281 Potential Cardiovascular Adverse Events in Phase 3 Studies

<b>List of Abbreviations and Definitions of Terms</b>	
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC <sub>∞</sub>	AUC from time zero to infinity
AUC <sub>∞,u</sub>	unbound AUC from time zero to infinity
BMI	body mass index
C <sub>max</sub>	maximum (peak) plasma concentration
C <sub>max, u</sub>	unbound maximum (peak) plasma drug concentration
C difficile	Clostridium difficile
COPD	chronic obstructive pulmonary disease
CYP1A2	cytochrome P450 isozyme 1A2
CYP2C9	cytochrome P450 isozyme 2C9
CYP2C19	cytochrome P450 isozyme 2C19
Dex	Dexlansoprazole
ECG	electrocardiogram
ECL	enterochromaffin-like
EE	erosive esophagitis
EGD	esophagogastroduodenoscopy
Est	estimated
Excl	excluding
F	female
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HLT	high level term
HTN	hypertension
IM	intestinal metaplasia
Incl	including
INR	international normalized ratio
INR <sub>144</sub>	area under the INR-time curve from time 0 to 144 hours postdose
INR <sub>max</sub>	maximum INR value observed from time 0 to 144 hours postdose
ISS	Integrated Summary of Safety
IV	intravenous
LLN	lower limit of normal
M	male
Min	minimum
MedDRA	Medical Dictionary for Regulatory Activities
Max	maximum
MR	modified release
MRI	magnetic resonance imaging
N	number of subjects
NEC	not elsewhere classified

<b>List of Abbreviations and Definitions of Terms</b>	
NSAID	nonsteroidal anti-inflammatory drug
Ong	ongoing
PCI	potentially clinically important
PCP	primary care physician
PD	pharmacodynamic or patient-days
PK	pharmacokinetic
PM	patient-months
PPI	proton pump inhibitor
QD	once daily
QID	four times a day
QT	duration of ventricular depolarization and subsequent repolarization, from the Q wave of the QRS complex and ending where the T wave returns to isoelectric baseline; the QT interval is inversely related to heart rate.
QTc	corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
SD	standard deviation
ULN	upper limit of normal
US	United States

***Appears This Way On Original***

**Table 7.1.1.2. Listing of Phase 3 Clinical Studies<sup>1</sup>**

Study ID Study Location(s)	Study Status Date of Study Start/Completion	Number of Study Sites Overall Enrollment Actual/Planned	Study Design Control Type	Study Objectives		Endpoints*
				Gender	Median Age (Range)	
T-EE04-084 United States, Australia, Bulgaria, Canada, Czech Republic, Estonia, Germany, India, Israel, Latvia, Lithuania, New Zealand, Poland, Russia, Slovakia, South Africa, and Ukraine	Complete	150	Randomized, double-blind, active-controlled	To assess the efficacy and safety in healing EE over 8 weeks of dexlansoprazole (60 mg QD and 90 mg QD) compared to lansoprazole delayed-release capsules (30 mg QD) in subjects with endoscopically proven EE; the secondary objectives were to assess the efficacy of dexlansoprazole (60 mg QD and 90 mg QD) compared to lansoprazole delayed-release capsule (30 mg QD) in healing EE over 4 weeks in subjects with endoscopically proven EE and in healing EE over 8 weeks in subjects with endoscopically proven moderate or severe EE.	Efficacy: the percentage of subjects who have complete healing of EE over 8 weeks as assessed by endoscopy. Safety: Adverse events, clinical laboratory values, gastrin levels, and vital signs.	
	Dec-05/Jan-07	2038/1950	Active			
	Study and Control Drugs Dose, Route, Regimen 60 mg oral dexlansoprazole: QD or 90 mg oral dexlansoprazole: QD or 30 mg oral lansoprazole delayed release QD	Subjects by Arm Entered/Completed 680/629 668/624 690/644	M/F 380/300 366/302 365/325	Duration of Treatment 4 or 8 weeks	Study Population and Primary Inclusion Criteria Males and females ≥18 years of age with endoscopically confirmed EE.	
T-EE04-085 USA, Australia, Bulgaria, Canada, Colombia, Czech Rep., Estonia, Germany, Hungary, India, Israel, Latvia, Lithuania, New Zealand, Peru, Poland, Russia, Slovakia, South Africa, Ukraine	Complete	156	Randomized, double-blind, active-controlled	To assess the efficacy and safety in healing EE over 8 weeks of dexlansoprazole (60 mg QD and 90 mg QD) in healing EE over 8 weeks in subjects with endoscopically proven EE; the secondary objectives were to assess the efficacy of dexlansoprazole (60 mg QD and 90 mg QD) compared to lansoprazole delayed-release capsules (30 mg QD) in healing EE over 4 weeks in subjects with endoscopically proven EE and in healing EE over 8 weeks in subjects with endoscopically proven moderate or severe EE.	Efficacy: The percentage of subjects who have complete healing of EE over 8 weeks as assessed by endoscopy. Safety: Adverse events, clinical laboratory values, gastrin levels, and vital signs.	
	Dec-05/Jan-07	2054/1950	Active			
	Study and Control Drugs Dose, Route, Regimen 60 mg oral dexlansoprazole: QD or 90 mg oral dexlansoprazole: QD or 30 mg oral lansoprazole delayed release QD	Subjects by Arm Entered/Completed 694/641 687/642 673/643	M/F 377/317 352/335 362/311	Duration of Treatment 4 or 8 weeks	Study Population and Primary Inclusion Criteria Males and females ≥18 years of age with endoscopically confirmed EE.	

<sup>1</sup> Sponsor's Table 2.7.y. from 2.7.4 Summary of Clinical Safety, pp.114-120.  
<sup>a</sup> If a study evaluated efficacy, only the primary endpoint(s) are listed.

**Table 7.1.1.2. Listing of Phase 3 Clinical Studies<sup>1</sup> (cont'd)**

Study ID Study Location(s)	Study Status Date of Study Start/Completion	Number of Study Sites Overall Enrollment Actual/Planned	Study Design Control Type	Study Objectives			Endpoints <sup>a</sup>
				Subjects by Arm Entered/Completed	Median Age (Range)	Duration of Treatment	
T-EE04-086  United States	Complete  Jan-06/Nov-06	105  451/450	Randomized, double-blind, placebo-controlled  Placebo	To assess the efficacy in maintenance of healed EE and safety of dexlansoprazole (60 mg QD and 90 mg QD) compared to placebo in subjects with healed EE; the secondary objectives were to assess the efficacy of dexlansoprazole (60 mg QD and 90 mg QD) compared to placebo in relief of daytime and nighttime heartburn over 6 months through the collection of daily diaries in subjects with healed EE.	Study Population and Primary Inclusion Criteria	Efficacy: The percentage of subjects who maintained healed EE over 6 months as assessed by endoscopy. Safety: Adverse events, physical examination, clinical laboratory values, serum gastrin levels, gastric biopsies, and vital signs.	
	Study and Control Drugs Dose, Route, Regimen  60 mg oral dexlansoprazole QD 90 mg oral dexlansoprazole QD oral placebo QD	Subjects by Arm Entered/Completed  159/110 152/103 140/17	Gender M/F  83/76 82/70 70/70	Median Age (Range)  49.0 (20-81) 51.0 (18-83) 48.0 (19-81)	Duration of Treatment  6 months	Study Population and Primary Inclusion Criteria  Males and females ≥18 years of age who successfully completed T-EE04-084 or T-EE04-085 with endoscopically proven healed EE requiring maintenance therapy.	
T-EE04-135  United States, Australia, Canada, the Czech Republic, Estonia, India, Latvia, Lithuania, Poland, and Slovakia	Complete  May-06/May-07	94  445/450	Randomized, double-blind, placebo-controlled  Placebo	To assess the efficacy in maintenance of healing and safety of dexlansoprazole (30 mg QD and 60 mg QD) compared to placebo in subjects with healed EE; the secondary objectives were to assess the efficacy of dexlansoprazole (30 mg QD and 60 mg QD) compared to placebo in relief of daytime and nighttime heartburn over 6 months through the collection of daily diaries in subjects with healed EE.	Study Population and Primary Inclusion Criteria	Efficacy: The percentage of subjects who maintained healed EE over 6 months as assessed by endoscopy. Safety: Adverse events, physical examination, clinical laboratory values, serum gastrin levels, gastric biopsies, and vital signs.	
	Study and Control Drugs Dose, Route, Regimen  30 mg oral dexlansoprazole QD 60 mg oral dexlansoprazole QD oral placebo QD	Subjects by Arm Entered/Completed  140/92 158/104 147/25	Gender M/F  69/71 74/84 72/75	Median Age (Range)  49.5 (21-85) 49.0 (22-78) 50.0 (18-84)	Duration of Treatment  6 months	Study Population and Primary Inclusion Criteria  Males and females who successfully completed T-EE04-084 or T-EE04-085 with endoscopically proven healed EE.	

<sup>1</sup> Sponsor's Table 2.7.y. from 2.7.4 Summary of Clinical Safety, pp.114-120.





Clinical Review of Safety  
Tamara Johnson, MD, MS  
NDA 022287  
KAPIDEX (Dexansoprazole)

(b) (4)



**Table 7.1.1.3. Brief Descriptions of Phase 1 Studies Conducted with Dexlansoprazole<sup>1</sup>**

Phase 1 Study	N	Dexlansoprazole MR Doses Evaluated (QD)	Comparator (QD)	Description
<b>Single-Dose</b>				
T-P104-069	25	90 mg	None	Food effect (pharmacokinetics only)
T-P104-092	34	90 and 300 mg	Placebo and Moxifloxacin 400 mg (positive control)	Effect on QT interval
T-P105-115	12	60 mg	None	Hepatic impairment
T-P105-119	23	60 mg	None	Age and gender
T-P106-146	46	90 mg	None	Food effect (pharmacokinetics/pharmacodynamics)
T-P106-148	60	90 mg	None	Bioavailability/bioequivalence (granules on applesauce versus intact capsule)
T-P106-149	53	90 mg	None	Bioavailability and pharmacokinetics of 3 different dexlansoprazole formulations
<b>Multiple-Dose</b>				
T-P104-071	31	60, 90, 120 mg	Lansoprazole 30 mg	Pharmacokinetics and pharmacodynamics
T-P104-100	40	90 and 120 mg	Lansoprazole 30 mg	Plasma gastrin concentration profile
T-P105-122	43	30 and 60 mg	Lansoprazole 15 mg	Pharmacokinetics and pharmacodynamics
T-P105-129	34	30, 60, and 90 mg	None	Pharmacokinetics in subjects with symptomatic GERD
T-P105-132	18	90 mg	Placebo	Effect on the pharmacokinetics and pharmacodynamics of warfarin
T-P105-133	16	90 mg	Placebo	Effect on the pharmacokinetics of phenytoin
T-P105-134	19	90 mg	Placebo	Effect on the pharmacokinetics of diazepam
T-P105-139	19	90 mg	Placebo	Effect on the pharmacokinetics of theophylline following single dose of aminophylline
T-P106-141	6	60 mg	None	Absorption, distribution, metabolism, excretion

<sup>1</sup> Sponsor's Table 2.7.a. from 2.7.4 Summary of Clinical Safety, p.13.

Table 7.3.1.2 Phase 3 Clinical Studies Deaths Listing (N=7)<sup>1,2</sup>

Trial	Patient ID	Age (yrs)	Sex	Cause of Death	Medical History	Study Day of Last Dose	Study Day of Death
TAK-390MR 60 MG QD							
T-GID04-082 GERD	11382007#	45	M	Acute Methadone Toxicity	White; History of hypertension, hypercholesterolemia, osteoarthritis, abdominal pain, heartburn, smoking 1 ½ packs/day x 25 yrs, and alcohol 1-7 drinks/week. The subject died unexpectedly in his sleep secondary to acute methadone toxicity, confirmed by autopsy.	14	17
T-EE04-084 Erosive esophagitis	32457009#	48	M	End Stage Liver Disease, Hepatic Coma & Malnutrition	White; history of alcohol abuse (initially reported sober 9 months) and recent hypokalemia, grade C erosive esophagitis, gastroesophageal reflux disease, cirrhosis, mild hepatitis and mild hepatic dysfunction. On Day 3, subject presented to ER with hypokalemia and progressively worsened with abdominal wound fistula, post procedural wound, peritonitis, septicemia, chronic respiratory failure, pneumonia and Guillain-Barre type syndrome until death.	3	88
T-EE04-085 Erosive esophagitis	11333014#	50	F	Stomach Cancer	Hispanic; History of hypertension, abdominal pain, abdominal cramping, diarrhea, unexplained weight loss and nodular mucosa of the antrum. The subject withdrew from the study due to nausea and epigastric pain. 72 days after the last dose of blinded study drug, the subject died from fatal stomach cancer. The investigator estimated the start date of the serious adverse event 54 days before the start of the study.	11	83

(b) (4)

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPIDEX (Dexlansoprazole)

Trial	Patient ID	Age (yrs)	Sex	Cause of Death	Medical History	Study Day of Last Dose	Study Day of Death
TAK-390MR 60 MG QD							

(b) (4)

LANSOPRAZOLE 30 MG QD							
T-EE04-084	32460061	58	F	Liposuction Surgery	Hispanic; History of hypertension, asthma and chronic obstructive pulmonary disease. The subject expired during liposuction surgery. The site reported the autopsy report and death certificate would not be available.	28	42

<sup>1</sup> Derived from sponsor's Table 7.1.2 List of Deaths in Phase 3 Studies, 5.3.5.3 Integrated Summary of Safety.

<sup>2</sup> Includes data from T-EE04-084, T-EE04-085, T-EE04-086, T-EE05-135, T-GD04-082, and T-GD05-137.

<sup>#</sup> Discontinued prematurely

<sup>a</sup> This subject previously had 29 days of exposure to placebo while enrolled in T-GD04-082.

<sup>b</sup> This subject previously had 27 days of exposure to placebo while enrolled in T-GD04-082.

<sup>c</sup> This subject had 123 days of total exposure to TAK-390MR 90 mg; 95 days of exposure to TAK-390MR in T-GH04-088 and 28 days of exposure to TAK-390MR 90 mg while enrolled in T-GD04-082.

**Table 7.3.2.5. Nonfatal Serious Adverse Events Considered Possibly Drug-Related in Phase 3 Trials<sup>1</sup>**

Subject No./ Gender/Age <sup>a</sup> / Study No.	MedDRA High Level Term/ MedDRA Preferred Term	Day of Onset <sup>b</sup>	Duration <sup>c</sup>	Relationship to Study Drug	Alternative Etiology
<b>Dexlansoprazole 60 mg QD</b>					
2954012/F/63/ T-EE04-085	Pain and Discomfort NEC/ Non-Cardiac Chest Pain	25 (0)	10 hours	Possible (+ dechallenge)	Hiatal hernia/ esophagitis
<b>Dexlansoprazole 90 mg QD</b>					
3000009/F/43/ T-EE04-085	Ischemic Coronary Artery Disorders/Arteriospasm Coronary	31	3	Possible	Known cardiac arrhythmia
31542001/F/46/ T-GI04-088	Perception Disturbances/ Hallucination, Auditory	11 (0)	Ongoing (175)	Possible	Schizoaffective disorder
32663005/F/60/ T-GI04-088	Pain and Discomfort NEC/ Chest Pain	265 (0)	5	Possible	GERD or study drug
<b>Lansoprazole 30 mg QD</b>					
32713022/F/56/ T-EE04-084	Central Nervous System Hemorrhages and Cerebrovascular Accidents/ Cerebrovascular Accident	42 (9)	1 hour	Not related	Previous brain hemorrhage and previous seizure
	Paralysis and Paresis (Excl Cranial Nerve)/Hemiparesis		Ongoing (192)	Possible	Cerebral vascular event secondary to HTN (prior history of HTN)
21013017/M/58/ T-EE04-085	Facial Cranial Nerve Disorder/Facial Palsy	6	Ongoing (54)	Possible	None/Left 7 cranial nerve palsy

<sup>1</sup> From sponsor's Tables 2.7.i. and 2.7.n. of 2.7.4. Summary of Clinical Safety, pp.43-4, 48-9.

<sup>a</sup> Age at time of enrollment.

<sup>b</sup> Relative to first day of dosing in Study. Days postdosing are shown in parentheses.

<sup>c</sup> Duration is in days unless otherwise noted. If the event was ongoing, the day at which it was ongoing is shown in parentheses.

**Table 7.3.2.6. Nonfatal Serious Adverse Event Listing in Phase 3 HEE Studies**

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/ MedDRA Preferred Term	Day of Onset	Duration	Relationship to Study Drug	Alternative Etiology	Tx Grp
12800003/F/59/ T-EE04-084	Pain and Discomfort NEC/Non- cardiac Chest Pain	20 (1)	3	Not related	Non-cardiac stress related pain	Dex 60 mg QD
32118017/M/5 1/ T-EE04-084	Transient Cerebrovascular Events/Transient Ischemic Attack	1 (0)	3	Not related	<b>Other – patient under care of cardiologist, neurologist, and primary care physician. Patient had magnetic resonance imaging of the brain and carotid Doppler.</b>	Dex 60 mg QD

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPIDEX (Dexlansoprazole)

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/ MedDRA Preferred Term	Day of Onset	Duratr n	Relationship to Study Drug	Alternative Etiology	Tx Grp
32457009/M/4 8/ T-EE04-084	Acute Polyneuropathies/Guillain- Barre Syndrome	3 (0)	Ong (88)	Not related	Viral syndrome	Dex 60 mg QD
	Potassium Imbalance/Hypokalemia	3 (0)	3	Not related	Hypokalemia from baseline	Dex 60 mg QD
	Intestinal Ulcers and Perforation NEC/Intestinal Perforation	11 (8)	<24 hours	Not related	Spontaneous colonic perforation	Dex 60 mg QD
	Peritoneal and Retroperitoneal Disorders/Peritonitis		Ong (88)	Not related	Bowel perforation	Dex 60 mg QD
	Sepsis, Bacteraemia and Respiratory Failures (Excl Neonatal)/Chronic Respiratory Failure	16 (13)	Ong (88)	Not related	Guillian-Barre type syndrome	Dex 60 mg QD
	Lower Respiratory Tract and Lung Infections/Pneumonia					Dex 60 mg QD
	Soft Tissue Disorders NEC/Fistula	25 (22)	Ong (88)	Not related	Due to abdominal wound infection	Dex 60 mg QD
	Infections NEC/Postoperative Wound Infection				Postoperative infection	Dex 60 mg QD
32957001/M/4 9/ T-EE04-084	Coronary Artery Disorders NEC/Coronary Artery Disease	66 (0)	10	Not related	Atherosclerosis coronary artery disease	Dex 60 mg QD
32999003/M/7 4/ T-EE04-084	Gastrointestinal Atonic and Hypomotility Disorders NEC/Gastroesophageal Reflux Disease	46 (20)	2	Not related	Gastro esophageal reflux disease	Dex 60 mg QD
13384024/F/64/ T-EE04-085	Breast and Nipple Neoplasms Malignant/Breast Cancer Female	17	Ong (134)	Not related	Family history	Dex 60 mg QD
4826023/F/38/ T-EE04-085	Site Specific Injuries NEC/Back Injury	29	Ong (32)	Not related	Fall at home	Dex 60 mg QD
	Non-Site Specific Injuries NEC/Fall				Slipped in bathroom	Dex 60 mg QD
2954012/F/63/ T-EE04-085	Pain and Discomfort NEC/ Non-Cardiac Chest Pain	25 (0)	10 hours	Possible	Hiatal hernia/ esophagitis	Dex 60 mg QD
32849038/M/6 7/ T-EE04-085	Ischemic Coronary Artery Disorders/ Acute Myocardial Infarction	47	5	Not related	Ischemic heart disease	Dex 60 mg QD
8515013/F/33/ T-EE04-084	Gastrointestinal Inflammatory Disorders NEC/Crohn's Disease	12	4	Not related	Candida or Crohn's disease	Dex 90 mg QD
9755050/M/85/ T-EE04-084	Hemorrhoids and Gastrointestinal Varices (Excl Esophageal)/ Hemorrhoids	3	4	Not related	Hospitalized, Hemorrhoidectom y surgery performed	Dex 90 mg QD

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPIDEX (Dexlansoprazole)

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/ MedDRA Preferred Term	Day of Onset	Duratr	Relationship to Study Drug	Alternative Etiology	Tx Grp
32413004/M/48/ T-EE04-085	Abdominal and Gastrointestinal Infections/Gastroenteritis	30	3	Not related	Subject ate some bad oysters	Dex 90 mg QD
32730005/F/39/ T-EE04-085	Renal Lithiasis/Nephrolithiasis	63 (28)	15	Not related	Underlying predisposition	Dex 90 mg QD
30000009/F/43/ T-EE04-085	Ischemic Coronary Artery Disorders/Arteriospasm Coronary	31	3	Possible	Known cardiac arrhythmia	Dex 90 mg QD
32468002/M/34/ T-EE04-085	Cholecystitis and Cholelithiasis/ Cholecystitis	27	4	Not related	Cholelithiasis	Dex 90 mg QD
9172118/F/70/ T-EE04-084	Duodenal and Small Intestinal Stenosis and Obstruction/Small Intestinal Obstruction	8	11	Not related	Adhesions	Lansoprazole 30 mg QD
32425016/M/66/ T-EE04-084	Cholecystitis and Cholelithiasis/ Cholecystitis	54	2	Not related	Possible cholecystitis, prior gallstone	Lansoprazole 30 mg QD
32460032/F/41/ T-EE04-084	Bipolar Disorders/Bipolar Disorder	42 (0)	8	Not related	Bipolar disorder	Lansoprazole 30 mg QD
32471003/M/66/ T-EE04-084	Streptococcal Infections/Pneumonia Streptococcal	12	30	Not related	Infectious	Lansoprazole 30 mg QD
32713022/F/56/ T-EE04-084	Central Nervous System Hemorrhages and Cerebrovascular Accidents/Cerebrovascular Accident	42 (9)	1 hour	Not related	Previous brain hemorrhage and previous seizure	Lansoprazole 30 mg QD
	Paralysis and Paresis (Excl Cranial Nerve)/Hemiparesis		Ong (192)	Possible	Cerebral vascular event second to HTN (prior history of HTN)	Lansoprazole 30 mg QD
21013017/M/58/ T-EE04-085	Facial Cranial Nerve Disorder/Facial Palsy	6	Ong (54)	Possible	None/Left 7 cranial nerve palsy	Lansoprazole 30 mg QD
32470006/M/75/ T-EE04-085	Cholecystitis and Cholelithiasis/ Cholecystitis	18	2	Not related	Cholecystitis	Lansoprazole 30 mg QD

Sponsor's Table 48, 5.3.5.3 Integrated Summary of Safety, pp.153-4.

**Table 7.3.2.7. Nonfatal Serious Adverse Event Listing in Phase 3 MHEE Studies**

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/MedDRA Preferred Term	Day of Onset	Duratr	Relationship to Study Drug	Alternative Etiology	Tx Grp
9172167/F/39d/ T-EE05-135	Abortions Spontaneous/ Abortion Spontaneous	190 (11)	6 hours	Not related	Rhesus negative	Placebo QD
32860001/M/56d,e,f/ T-EE05-135	Prostatic Neoplasms Malignant/Prostate Cancer Stage I	157 (0)	22	Not related	Population exposure	Dex 30 mg QD

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPIDEX (Dexlansoprazole)

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/MedDRA Preferred Term	Day of Onset	Duratn	Relationship to Study Drug	Alternative Etiology	Tx Grp
9172128/F/44d,f/ T-EE05-135	Abortions Spontaneous/ Abortion Spontaneous	102 (6)	1 hour	Not related	Possible gynecological abnormality	Dex 30 mg QD
12455031/F/39e/ T-EE05-135	Cholecystitis and Cholelithiasis/Cholecystitis	2	4	Not related	Obesity	Dex 60 mg QD
	Uterine Disorders NEC/Endometriosis	150	32	Not related	Has current condition of endometriosis	Dex 60 mg QD
	Ovarian and Fallopian Tube Cysts and Neoplasms/Ovarian Cyst	150	32	Not related	History of ovarian cysts	Dex 60 mg QD
13239063/M/31d,f/ T-EE05-135	Bronchospasm and Obstruction/Bronchospasm	88	7 minutes	Not related	Bronchospasm due to EGD	Dex 60 mg QD
14763134/F/62e/ T-EE05-135	Pain and Discomfort NEC/Non-Cardiac Chest Pain	156	5	Not related	Chest pain secondary to GERD	Dex 60 mg QD
18128010/F/45e/ T-EE04-086	Uterine Disorders NEC/Endometriosis	77	1 hour	Not related	Endometriosis	Dex 60 mg QD
13239048/F/62e/ T-EE04-087	Pain and Discomfort NEC/ Non-Cardiac Chest Pain	48	3	Not related	Bronchospasm; obesity; esophagitis	Dex 60 mg QD
21368058/F/41d,f/ T-EE05-135	Migraine Headaches/Migraine	148	10	Not related	History of migraines	Dex 60 mg QD
	Implant and Catheter Site Reactions/Catheter Related Complication	164	145	Not related	PICC line placement	Dex 60 mg QD
	Bacterial Infections NEC/Cellulitis	164	145	Not related	Secondary to migraine therapy	Dex 60 mg QD
	Peripheral Embolism and Thrombosis/Deep Vein Thrombosis	164	145	Not related	Hospitalization and drug therapy	Dex 60 mg QD
	Peripheral Embolism and Thrombosis/Thrombophlebit is Superficial	164	145	Not related	Hospital and drug therapy	Dex 60 mg QD
	Viral Infections NEC/Gastroenteritis Viral	187 (12)	122	Not related	Virus	Dex 60 mg QD
7315029/M/23e,f,g/ T-EE05-135	Cerebrovascular Venous and Sinus Thrombosis/Cerebral Venous Thrombosis	180 (1)	Ong (209)	Not related	Congenital	Dex 60 mg QD
9172137/M/29e,f/ T-EE05-135	Non-Site Specific Injuries NEC/Injury	51 est	1 minute	Not related	Activity	Dex 60 mg QD
	Limb Injuries NEC (Incl Traumatic Amputation)/ Limb Injury	51 est	Unknow n	Not related	Activity	Dex 60 mg QD

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPIDEX (Dexlansoprazole)

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/MedDRA Preferred Term	Day of Onset	Duratn n	Relationship to Study Drug	Alternative Etiology	Tx Grp
9624010/F/66d,f/ T-EE04-086	Breast and Nipple Neoplasms Malignant/Breast Cancer	1	Chronic Conditio n	Not related	Family history of breast cancer	Dex 90 mg QD
9677008/M/54e/ T-EE04-086	Non-site Specific Injuries NEC/Arthropod Bite	89	18	Not related	Spider bite	Dex 90 mg QD
12823011/F/28d/ T- EE04-086	Musculoskeletal and Connective Tissue Signs and Symptoms NEC/ Musculoskeletal Discomfort	126	29	Not related	Weight of breast tissue	Dex 90 mg QD
18128038/M/62d,e,f/ T-EE04-086	Coronary Artery Disorders NEC/ Coronary Artery Disease	6 (1)	3	Not related	Past history of coronary artery disease	Dex 90 mg QD
9172053/F/54e,f/ T-EE04-086	Acute and Chronic Pancreatitis/ Pancreatitis	149	6	Not related	Gallstones	Dex 90 mg QD

Sponsor's Table 50, 5.3.5.3 Integrated Summary of Safety, pp.158-9.

**Table 7.3.2.8. Nonfatal Serious Adverse Event Listing in Phase 3 GERD Studies**

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/MedDRA Preferred Term	Day of Onset	Duration	Relationship to Study Drug	Alternative Etiology	Tx Grp
31989003/F/56/ T-GD05-137	Coronary Artery Disorders NEC/ Coronary Artery Occlusion	25 (0)	3	Not related	Secondary to Type II diabetes, hypertension, and hypercholesterolemia	Placebo QD
32454009/F/71/ T-GD05-137	Ischemic Coronary Artery Disorders/Myocardial Infarction	27 (4)	20	Not related	Arteriosclerosis, secondary to hypertension and diabetes	Dex 30 mg
	Central Nervous System Hemorrhages and Cerebrovascular Accidents/Cerebrovascular Accident	30 (7)	Ongoing (73)	Not related	Status post-surgery (coronary artery bypass surgery)	Dex 30 mg QD
9319002/M/60/ T-GD05-137	Ischemic Coronary Artery Disorders/Myocardial Infarction	30 (2)	30	Not related	Atherosclerosis	Dex 30 mg QD
	Heart Failures NEC/Cardiogenic Shock	31(3)	29	Not related	Myocardial infarction	Dex 30 mg QD
	Sepsis, Bacteremia, Viraemia And Fungaemia NEC/Sepsis	31(3)	29	Not related	Myocardial infarction	Dex 30 mg QD
9677036/F/56/ T-GD05-137	Gastrointestinal and Abdominal Pains (Excl Oral and Throat)/ Abdominal Pain Lower	16	3	Not related	Bleeding from colon	Dex 60 mg QD

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPIDEX (Dexlansoprazole)

	Non-site Specific Gastrointestinal Hemorrhages/Hematochezia	16	3	Not related	Bleeding from polyp removal	Dex 60 mg QD
14763033/F/53/ T-GD04-083	Non-site Specific Injuries NEC/ Foreign Body Trauma	6	7	Not related	Foreign object (suture) in bladder	Dex 60 mg QD
32468017/F/49/ T-GD04-083	Cholecystitis and Cholelithiasis/ Cholecystitis Chronic	25	2	Not related	Cholelithiasis	Dex 90 mg QD

Sponsor's Table 46, 5.3.5.3 Integrated Summary of Safety, p.149.

**Table 7.3.2.9. Nonfatal Serious Adverse Event Listing in Phase 3 LTS Study  
 (Cutoff Date: Jan 2008)**

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/ MedDRA Preferred Term	Day of Onset	Duratr n	Relationship to Study Drug	Alternative Etiology	Tx Grp
12453008/M/44/ T- GI04-088	Upper Respiratory Tract Infections/Sinusitis	31	16	Not related	Influenza and pansinusitis	Dex 60 mg QD
20986004/F/36/ T- GI04-088	Cholecystitis and Cholelithiasis/ Cholelithiasis	70	4	Not related	Obesity	Dex 60 mg QD
22438008/F/65/ T- GI04-088	Disturbances in Consciousness NEC/Syncope	99	3	Not related	Sinus ventricular tachycardia	Dex 60 mg QD
	Abdominal and Gastrointestinal Infections/Diverticulitis	186	4	Not related	Inflammation	Dex 60 mg QD
29061005/F/36/ T- GI04-088	Uterine Neoplasms Benign/ Uterine Leiomyoma	134	4	Not related	Idiopathic	Dex 60 mg QD
32445001/M/55/ T- GI04-088	Abdominal and Gastrointestinal Infections/Gastroenteritis	62	4	Not related	Viral	Dex 60 mg QD
9172011/F/58/ T- GI04-088	Bronchospasm and Obstruction/ Asthma	13 (0)	7	Not related	Pneumonia induced	Dex 60 mg QD
9172011/F/58/ T- GI04-088	Lower Respiratory Tract and Lung Infections/Pneumonia	13 (0)	7	Not related	Bacterial	Dex 60 mg QD
9756006/F/39/ T- GI04-088	Migraine Headaches/Migraine	83	48	Not related	Congenital anomaly	Dex 60 mg QD
11376005/F/49/ T- GI04-088	Cholecystitis and Cholelithiasis/ Cholecystitis	151	2	Not related	Gallstones	Dex 90 mg QD
12800007/F/77/ T- GI04-088	Non-Site Specific Injuries NEC/ Fall	231	3 seconds	Not related	Patient fell due to slippery conditions-no dizziness reported- no dizziness reported	Dex 90 mg QD
	Lower Limb Fractures and Dislocations/Ankle Fracture	239	4 hours	Not related	Slippery conditions due to weather	Dex 90 mg QD
12818005/F/75/ T- GI04-088	Inner Ear Signs and Symptoms/ Vertigo Positional	21	4	Not related	History of acoustic neuroma	Dex 90 mg QD
21457011/F/59/ T- GI04-088	Non-Site Specific Injuries NEC/ Fall	94	1 minute	Not related	Slippery ladder	Dex 90 mg QD

Clinical Review of Safety  
 Tamara Johnson, MD, MS  
 NDA 022287  
 KAPIDEX (Dexlansoprazole)

Subject No./ Gender/Age/ Study No.	MedDRA High Level Term/ MedDRA Preferred Term	Day of Onset	Duratr n	Relationship to Study Drug	Alternative Etiology	Tx Grp
21457011/F/59/ T- GI04-088	Pneumothorax and Pleural Effusions NEC/Pneumothorax	94	7	Not related	Fall	Dex 90 mg QD
21457011/F/59/ T- GI04-088	Thoracic Cage Fractures and Dislocations/Rib Fracture	94	7	Not related	Fall	Dex 90 mg QD
31542001/F/46/ T- GI04-088	Perception Disturbances/ Hallucination, Auditory	11 (0)	Ong (175)	Possible	Schizoaffective disorder	Dex 90 mg QD
32128009/F/73/ T- GI04-088	Non-Site Specific Injuries NEC/ Fall	347	1.0 hour	Not related	Inclement weather	Dex 90 mg QD
32128009/F/73/ T- GI04-088	Pain and Discomfort NEC/ Non- Cardiac Chest Pain	347	43	Not related	Fall on ice	Dex 90 mg QD
32420010/F/48/ T- GI04-088	Disturbances in Consciousness NEC/Syncope	17	6	Not related	History of blood pressure fluctuations and syncope	Dex 90 mg QD
	Urinary Tract Infections/ Urinary Tract Infection	217	7	Not related	Subject is diabetic	Dex 90 mg QD
32663005/F/60/ T- GI04-088	Pain and Discomfort NEC/ Chest Pain	265 (0)	5	Possible	GERD or study drug	Dex 90 mg QD
9172013/F/64/ T- GI04-088	Non-Site Specific Injuries NEC/ Fall	95	1 second	Not related	Accident	Dex 90 mg QD
9172013/F/64/ T- GI04-088	Upper Limb Fractures and Dislocations/Upper Limb Fracture	95	11	Not related	Fall	Dex 90 mg QD
9763001/F/58/ T- GI04-088	Pulmonary Thrombotic and Embolic Conditions/Pulmonary Embolism	12 (0)	10 hours	Not related	Knee hi stocking and feminine hormone replacement therapy	Dex 90 mg QD
31023301/M/50# / T- GI04-088	Intervertebral Disc Disorders NEC/Intervertebral Disc Protrusion	65	2	Not related	Trauma to the back	Dex 90 mg QD
32470309/M/47# / T- GI04-088	Renal Lithiasis/ Nephrolithiasis	26	2	Not related	Flank pain	Dex 90 mg QD
8417313/F/76 / T- GI04-088	Cholecystitis and Cholelithiasis/Cholelithiasis <sup>b</sup>	80	5	Possible	Age-, dietary-, and hereditary-related factors	Dex 90 mg QD
8417313/F/76 / T- GI04-088	Cholecystitis and Cholelithiasis/Cholecystitis Acute <sup>b</sup>	80	5	Possible	Age-, dietary-, and hereditary-related factors	Dex 90 mg QD
11371304/F/59 / T- GI04-088	Intervertebral Disc Disorders NEC/Intervertebral Disc Protrusion	87	53	Not related	Disc was bulging and then ruptured on its own	Dex 90 mg QD
12814306/F/51# / T- GI04-088	Neutropenias/Febrile Neutropenia <sup>c</sup>	212	7	Possible	Antibiotic (Bactrim)	Dex 90 mg QD
32470305/F/81# / T- GI04-088	B-Cell Lymphomas NEC/ B-Cell Lymphoma	210	Ong (253)	Possible	Unknown cause of a malignant B-cell lymphoma	Dex 90 mg QD
32470309/M/47# / T- GI04-088	Renal Cell Carcinomas/Renal Cell Carcinoma State Unspecified	60	159	Not related	Unknown cause for renal cell carcinoma	Dex 90 mg QD

Clinical Review of Safety  
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 NDA 022287  
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9172316/F/64 / T- GI04-088	Joint Related Disorders NEC/ Joint Instability	84	77	Not related	Degenerative joint disease	Dex 90 mg QD
21457305/F/34#/ T- GI04-088	Anaphylactic Responses/ Anaphylactic Reaction	305	<1	Possible	Celebrex	Dex 90 mg QD
9172315/M/80 / T- GI04-088	Neoplasms Malignant Site Unspecified NEC/Squamous Cell Carcinoma	182	42	Not related	Sun exposure	Dex 90 mg QD

Derived Sponsor's Table 52, 5.3.5.3 Integrated Summary of Safety, pp.163-164, and Tables 14-16, 5.3.5.4. 4-  
 Month Safety Update, pp.55-56.

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