

**Table 7.3.4.1.4. Potential Cardiovascular Adverse Events per 100PM of Exposure in Phase 3 Studies<sup>1</sup>**

	Treatment Group: n (rate per 100 PM)										
	Placebo (N=896) (AVG PM=1.2)	Dexlansoprazole					Lansoprazole 30 mg (N=1363) (AVG PM=1.3)				
		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>MedDRA High Level Term Preferred Term</b>											
<b>Neurological Signs and Symptoms</b>											
NEC	3 (0.28)	3 (0.32)	17 (0.32)	12 (0.29)	16 (0.27)	32 (0.31)	36 (0.30)	11 (0.61)			
Dizziness	3 (0.28)	3 (0.32)	17 (0.32)	12 (0.29)	16 (0.27)	32 (0.31)	36 (0.30)	11 (0.61)			
<b>Oedema NEC</b>	5 (0.47)	3 (0.32)	19 (0.36)	12 (0.29)	13 (0.22)	34 (0.33)	35 (0.29)	5 (0.28)			
Oedema	0	0	1 (0.02)	2 (0.05)	2 (0.03)	3 (0.03)	3 (0.02)	0			
Oedema Peripheral	5 (0.47)	2 (0.21)	16 (0.30)	10 (0.24)	11 (0.18)	28 (0.27)	29 (0.24)	5 (0.28)			
Pitting Oedema	0	1 (0.11)	2 (0.04)	0	0	3 (0.03)	3 (0.02)	0			
<b>Pain and Discomfort NEC</b>	2 (0.19)	4 (0.43)	8 (0.15)	8 (0.19)	9 (0.15)	20 (0.19)	21 (0.17)	3 (0.17)			
Chest Pain	2 (0.19)	4 (0.43)	8 (0.15)	8 (0.19)	9 (0.15)	20 (0.19)	21 (0.17)	3 (0.17)			
<b>Ischaemic Coronary Artery Disorders</b>	0	3 (0.32)	2 (0.04)	1 (0.02)	1 (0.02)	6 (0.06)	6 (0.05)	0			
Acute Myocardial Infarction	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)	0			
Angina Pectoris	0	1 (0.11)	0	0	0	1 (<0.01)	1 (<0.01)	0			
Arteriospasm Coronary	0	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	0			
Myocardial Infarction	0	2 (0.21)	0	0	0	2 (0.02)	2 (0.02)	0			
Myocardial Ischaemia	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)	0			
<b>Vascular Hypertensive Disorders</b>											
NEC	2 (0.19)	2 (0.21)	16 (0.30)	7 (0.17)	9 (0.15)	25 (0.24)	27 (0.22)	5 (0.28)			
Essential Hypertension	0	0	1 (0.02)	0	0	1 (<0.01)	1 (<0.01)	0			
Hypertension	2 (0.19)	2 (0.21)	15 (0.28)	7 (0.17)	9 (0.15)	24 (0.23)	26 (0.21)	4 (0.22)			
Labile Hypertension	0	0	0	0	0	0	0	1 (0.06)			
<b>Breathing Abnormalities</b>	3 (0.28)	0	7 (0.13)	4 (0.10)	4 (0.07)	11 (0.11)	11 (0.09)	0			
Dyspnoea	3 (0.28)	0	7 (0.13)	4 (0.10)	4 (0.07)	11 (0.11)	11 (0.09)	0			
Hyperventilation	0	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	0			
<b>Heart Failures NEC</b>	0	2 (0.21)	1 (0.02)	0	0	3 (0.03)	3 (0.02)	0			

Cardiac Failure	0	0	1 (0.02)	0	0	0	1 (<0.01)	0	1 (<0.01)	0
Cardiac Failure Congestive	0	1 (0.11)	0	0	0	0	1 (<0.01)	0	1 (<0.01)	0
Cardiogenic Shock	0	1 (0.11)	0	0	0	0	1 (<0.01)	0	1 (<0.01)	0
Cardiac Signs and Symptoms NEC	2 (0.19)	1 (0.11)	5 (0.09)	3 (0.07)	3 (0.05)	3 (0.05)	9 (0.09)	9 (0.07)	9 (0.07)	0
Palpitations	2 (0.19)	1 (0.11)	5 (0.09)	3 (0.07)	3 (0.07)	3 (0.05)	9 (0.09)	9 (0.07)	9 (0.07)	0
Vascular Tests NEC (Incl Blood Pressure)	2 (0.19)	1 (0.11)	2 (0.04)	3 (0.07)	4 (0.07)	4 (0.07)	6 (0.06)	7 (0.06)	7 (0.06)	0
Blood Pressure Increased	2 (0.19)	1 (0.11)	2 (0.04)	3 (0.07)	4 (0.07)	4 (0.07)	6 (0.06)	7 (0.06)	7 (0.06)	0
General Signs and Symptoms NEC	0	1 (0.11)	7 (0.13)	6 (0.15)	7 (0.12)	7 (0.12)	14 (0.14)	15 (0.12)	15 (0.12)	0
Chest Discomfort	0	1 (0.11)	7 (0.13)	6 (0.15)	7 (0.12)	7 (0.12)	14 (0.14)	15 (0.12)	15 (0.12)	0
Vascular Hypotensive Disorders	0	1 (0.11)	0	0	0	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	2 (0.11)
Hypotension	0	1 (0.11)	0	0	0	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	2 (0.11)
Central Nervous System Haemorrhages and Cerebrovascular Accidents	0	1 (0.11)	0	1 (0.02)	1 (0.02)	1 (0.02)	2 (0.02)	2 (0.02)	2 (0.02)	1 (0.06)
Cerebral Ischaemia	0	0	0	1 (0.02)	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Cerebrovascular Accident	0	1 (0.11)	0	0	0	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	1 (0.06)
EKG Investigations	1 (0.09)	1 (0.11)	0	1 (0.02)	1 (0.02)	1 (0.02)	2 (0.02)	2 (0.02)	2 (0.02)	0
Electrocardiogram Change	0	1 (0.11)	0	0	0	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Electrocardiogram Low Voltage	0	0	0	1 (0.02)	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Electrocardiogram QT/QTc Corrected Interval Prolonged	1 (0.09)	0	0	0	0	0	0	0	0	0
QRS Axis Abnormal	0	0	0	1 (0.02)	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Rate and Rhythm Disorders NEC	0	1 (0.11)	4 (0.08)	0	0	0	5 (0.05)	5 (0.04)	5 (0.04)	0
Arrhythmia	0	0	1 (0.02)	0	0	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Bradycardia	0	1 (0.11)	0	0	0	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Tachycardia	0	0	3 (0.06)	0	0	0	3 (0.03)	3 (0.02)	3 (0.02)	0
Ventricular Arrhythmias and Cardiac Arrest	0	1 (0.11)	0	0	0	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Ventricular Extrasystoles	0	1 (0.11)	0	0	0	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Coronary Artery Disorders NEC	1 (0.09)	0	1 (0.02)	2 (0.05)	2 (0.03)	2 (0.03)	3 (0.03)	3 (0.02)	3 (0.02)	0
Coronary Artery Disease	1 (0.09)	0	1 (0.02)	2 (0.05)	2 (0.03)	2 (0.03)	3 (0.03)	3 (0.02)	3 (0.02)	0
Coronary Artery Occlusion	1 (0.09)	0	0	0	0	0	0	0	0	0
Supraventricular Arrhythmias	1 (0.09)	0	0	2 (0.05)	2 (0.03)	2 (0.03)	2 (0.02)	2 (0.02)	2 (0.02)	1 (0.06)

Sinus Tachycardia	0	0	2 (0.05)	2 (0.03)	2 (0.02)	2 (0.02)	0	0
Supraventricular Extrasystoles	1 (0.09)	0	0	0	0	0	0	0
Supraventricular Tachycardia	0	0	0	0	0	0	0	1 (0.06)
<b>Accelerated and Malignant Hypertension</b>	0	0	0	0	0	0	0	1 (0.06)
Hypertensive Crisis	0	0	0	0	0	0	0	1 (0.06)
<b>Coughing and Associated Symptoms</b>	0	0	1 (0.02)	2 (0.03)	2 (0.02)	3 (0.02)	3 (0.02)	1 (0.06)
Haemoptysis	0	0	1 (0.02)	2 (0.03)	2 (0.02)	3 (0.02)	3 (0.02)	1 (0.06)
<b>Disturbances In Consciousness NEC</b>	0	0	1 (0.02)	1 (0.02)	3 (0.03)	3 (0.02)	3 (0.02)	1 (0.06)
Syncope	0	0	1 (0.02)	1 (0.02)	3 (0.03)	3 (0.02)	3 (0.02)	0
Syncope Vasovagal	0	0	0	0	0	0	0	1 (0.06)
<b>Peripheral Embolism and Thrombosis</b>	0	0	1 (0.02)	2 (0.03)	3 (0.03)	3 (0.02)	3 (0.02)	1 (0.06)
Deep Vein Thrombosis	0	0	1 (0.02)	2 (0.03)	3 (0.03)	3 (0.02)	3 (0.02)	1 (0.06)
Thrombophlebitis Superficial	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	1 (0.06)
<b>Total Fluid Volume Increased</b>	0	0	1 (0.02)	2 (0.03)	1 (<0.01)	2 (<0.02)	2 (<0.02)	1 (0.06)
Fluid Retention	0	0	1 (0.02)	2 (0.03)	1 (<0.01)	2 (<0.02)	2 (<0.02)	1 (0.06)
<b>Phlebitis NEC</b>	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Phlebitis	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
<b>Pulmonary Oedemas</b>	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Pulmonary Oedema	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
<b>Pulmonary Thrombotic and Embolic Conditions</b>	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Pulmonary Embolism	0	0	1 (0.02)	1 (0.02)	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
<b>Cardiac Conduction Disorders</b>	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Bundle Branch Block Left	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Bundle Branch Block Right	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
<b>Cardiac Disorders NEC</b>	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Cardiac Disorder	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
<b>Cardiac Valve Disorders NEC</b>	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Cardiac Valve Disease	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
<b>Cerebellar Coordination and Balance Disturbances</b>	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0
Coordination Abnormal	0	0	1 (0.02)	0	1 (<0.01)	1 (<0.01)	1 (<0.01)	0

<b>Cerebrovascular Venous and Sinus Thrombosis</b>	0	0	1 (0.02)	0	0	1 (<0.01)	0	1 (<0.01)	0	0
Cerebral Venous Thrombosis	0	0	1 (0.02)	0	0	1 (<0.01)	0	1 (<0.01)	0	0
<b>Non-Site Specific Necrosis and Vascular Insufficiency NEC</b>	0	0	1 (0.02)	0	0	1 (<0.01)	0	1 (<0.01)	0	0
Arteriosclerosis	0	0	1 (0.02)	0	0	1 (<0.01)	0	1 (<0.01)	0	0
<b>Peripheral Vasoconstriction, Necrosis and Vascular Insufficiency</b>	0	0	1 (0.02)	0	0	1 (<0.01)	0	1 (<0.01)	0	0
Arteriosclerosis Obliterans	0	0	1 (0.02)	0	0	1 (<0.01)	0	1 (<0.01)	0	0
<b>Transient Cerebrovascular Events</b>	0	0	1 (0.02)	0	0	1 (<0.01)	0	1 (<0.01)	0	0
Transient Ischaemic Attack	0	0	1 (0.02)	0	0	1 (<0.01)	0	1 (<0.01)	0	0
<b>Heart Rate and Pulse Investigations</b>	0	0	0	0	1 (0.02)	0	0	1 (<0.01)	0	0
Heart Rate Increased	0	0	0	0	1 (0.02)	0	0	1 (<0.01)	0	0

<sup>1</sup> Sponsor's Table 24 from 5.3.5.4. 4-Month Safety Update, p. 79-85.

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## 9.1 Literature Review/References

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Pezalla E, Day D, Pulliadath I. Initial Assessment of Clinical Impact of a Drug Interaction Between Clopidogrel and Proton Pump Inhibitors. *J Am Coll Cardiol* 2008:1038-1039.

Richards JB, Goltzman D. Proton pump inhibitors: balancing the benefits and potential fracture risks. *CMAJ.* 2008 Aug 12;179(4):306-7.

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Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ.* 2008 Aug 12;179(4):319-26.

Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA.* 2006;296(24):2947-2953.

## 9.2 Labeling Recommendations

*The medical officer has the following comments and recommendations for the HIGHLIGHTS, INDICATIONS AND USAGE, ADVERSE REACTIONS, and CLINICAL STUDIES section of the dexlansoprazole label. Additionally, all references to the (b) (4) [REDACTED] have been removed from the label, as well as presentation of (b) (4) [REDACTED]. See the label text below.*

# 11 Page(s) Withheld

           Trade Secret / Confidential (b4)

  √   Draft Labeling (b4)

           Draft Labeling (b5)

           Deliberative Process (b5)

(b) (4)

[Redacted text block]

### 9.3 Regulatory Briefing

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

<p><b><u>Regulatory Briefing Questions</u></b></p> <p>1 Do you have concerns on the excess adverse events (AE) observed in the dexlansoprazole treatment groups compared to the lansoprazole or placebo group in Phase 3 studies?</p> <ul style="list-style-type: none"><li>a. Serious adverse events</li><li>b. Cardiovascular events</li><li>c. Fractures/injury-related events</li></ul> <p>2. What is your recommendation for regulatory action?</p> <ul style="list-style-type: none"><li>a. Complete Response with additional study to evaluate the potential AE</li><li>b. Approval without additional study</li><li>c. Approval with PMR for additional study to evaluate the potential AE</li></ul> <p>3. What types of study do you recommend, if additional study is needed?</p>
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The regulatory briefing panel, composed of CDER senior management officials, acknowledged the imbalance of adverse events between dexlansoprazole and its comparators in regards to

cardiovascular and fracture/injury-related events. Their recommendation for regulatory action focused, however, on the incidence of serious adverse events in these categories. The panel recommended approval without additional study. They additionally recommended approval of the lowest safe and effective dose of dexlansoprazole, per indication. This thereby would exclude the 90mg dosage (HEE) and 60mg dosage (MHEE) from approval.

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## CLINICAL REVIEW

Application Type NDA  
Submission Number 22-287  
Submission Code 000

Letter Date 31 Dec 2007  
Stamp Date 31 Dec 2007  
PDUFA Goal Date 31 Oct 2008

Reviewer Name Keith B. St. Amand, MD  
Review Completion Date 29 Aug 2008

Established Name Dexlansoprazole  
(Proposed) Trade Name (b) (4)  
Therapeutic Class Proton pump inhibitor (PPI)  
Applicant TAP Pharmaceuticals

Priority Designation S

Formulation Capsule  
Dosing Regimen 30/60 (b) (4) mg QD  
Indication Healing of erosive esophagitis;  
Maintenance of healing of erosive  
esophagitis;  
Treatment of (b) (4)  
heartburn (b) (4)  
associated with GERD

Intended Population Adults

**Table of Contents**

**1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....4**

1.1 Recommendation on Regulatory Action.....4

1.2 Risk Benefit Assessment .....5

1.3 Recommendations for Postmarketing Risk Management Activities .....6

1.4 Recommendations for other Post Marketing Study Commitments .....6

**2 INTRODUCTION AND REGULATORY BACKGROUND.....6**

2.1 Product Information.....6

2.2 Tables of Currently Available Treatments for Proposed Indications.....8

2.3 Availability of Proposed Active Ingredient in the United States.....10

2.4 Important Safety Issues With Consideration to Related Drugs .....11

2.5 Summary of Presubmission Regulatory Activity Related to Submission.....11

2.6 Other Relevant Background Information .....11

**3 ETHICS AND GOOD CLINICAL PRACTICES .....12**

3.1 Submission Quality and Integrity .....12

3.2 Compliance with Good Clinical Practices .....12

3.3 Financial Disclosures.....12

**4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....13**

4.1 Chemistry Manufacturing and Controls .....13

4.2 Preclinical Pharmacology/Toxicology.....13

4.3 Clinical Pharmacology .....14

**5 SOURCES OF CLINICAL DATA .....15**

5.1 Tables of Clinical Studies .....15

5.2 Review Strategy.....28

5.3 Discussion of Individual Studies .....28

**6 REVIEW OF EFFICACY .....28**

6.1 Healing of Erosive Esophagitis (HEE).....30

6.1.1 Methods .....30

6.1.2 Demographics/Baseline Characteristics.....37

6.1.3 Drug Exposure/Compliance/Patient Disposition .....41

6.1.4 Analysis of Primary Endpoint.....44

6.1.5 Analysis of Secondary Endpoints .....47

6.1.6 Subpopulations .....50

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations .....52

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects.....52

6.1.9 Additional Efficacy Issues/Analyses .....52

6.2 Maintenance of healing of erosive esophagitis (MHEE).....53

6.2.1 Methods .....53

6.2.2 Demographics/Baseline Characteristics.....58

6.2.3 Drug Exposure/Compliance/Patient Disposition .....63

6.2.4 Analysis of Primary Endpoint.....65

6.2.5 Analysis of Secondary Endpoints .....71

6.2.6 Subpopulations .....74

6.2.7 Analysis of Clinical Information Relevant to Dosing Recommendations .....77

6.2.8 Discussion of Persistence of Efficacy and/or Tolerance Effects.....78

6.2.9 Additional Efficacy Issues/Analyses .....78

6.3 Treatment of GERD.....79

6.3.1 Methods .....79

Clinical Review  
Keith B. St. Amand, MD  
NDA 22-287

**(b)** (dexlansoprazole)

6.3.2	Demographics/Baseline Characteristics.....	86
6.3.3	Drug Exposure/Compliance/Patient Disposition .....	89
6.3.4	Analysis of Primary Endpoint.....	91
6.3.5	Analysis of Secondary Endpoints .....	94
6.3.6	Subpopulations .....	96
6.3.7	Analysis of Clinical Information Relevant to Dosing Recommendations .....	98
6.3.8	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	98
6.3.9	Additional Efficacy Issues/Analyses .....	99
<b>7</b>	<b>APPENDICES .....</b>	<b>101</b>
7.1	Literature Review/References .....	101
7.2	Labeling Recommendations .....	102

***Appears This Way On Original***

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

*Note: The following recommendations are based solely on the reviewer's assessment of the efficacy of dexlansoprazole. Since significant safety concerns are present with this product, please see Section 1.2 below for the reviewer's overall risk/benefit assessment and recommendation.*

Proposed Indication: Healing **(b) (4)** of all grades of erosive esophagitis

- From an efficacy standpoint, the reviewer recommends approval of **(b) (4)** the 60 mg **(b) (4)** doses of dexlansoprazole for this indication.
- Both dex 60 mg and 90 mg were non-inferior to lansoprazole 30 mg and a labeling claim to this effect is acceptable.
- Although dex 90 mg showed statistical superiority over lansoprazole 30 mg, the reviewer does not believe this difference is clinically meaningful **(b) (4)**
- **(b) (4)**
- **(b) (4)** (the 90 mg dose relies on a pooled analysis, and the 60 mg dose only shows a significant difference in one study).
- **(b) (4)**
- The language **(b) (4)** should be removed from the indication as it is based on exploratory endpoints; "healing of all grades of erosive esophagitis" is acceptable.

Proposed Indication: Maintenance of healing of erosive esophagitis **(b) (4)**

- From an efficacy standpoint, the reviewer recommends approval of **(b) (4)** the 30 mg **(b) (4)** dose of dexlansoprazole for this indication.
- Both doses showed clear superiority over placebo **(b) (4)**
- No superiority was seen for the 60 mg dose of dex over the 30 mg dose, either for the overall patient population or for any subgroups, and no labeling claim to this effect should be permitted. However, the clinical study results could be presented in an appropriate section of the label (i.e., Clinical Studies) to provide more detailed information regarding the comparison of the two doses.

• **(b) (4)**

(b) (4) (dexlansoprazole)

- The language (b) (4) is based on key secondary endpoints for which a statistically significant difference was seen for both dex doses when compared to placebo. Claims to this effect could be presented in labeling if the Biostatistics reviewers agree that the sponsor's hierarchical plan for assessing these secondary endpoints is sound.

Proposed Indication: Treatment of (b) (4) heartburn (b) (4) associated with gastroesophageal reflux disease (sGERD)

- From an efficacy standpoint, the reviewer recommends approval of the 30 mg dose of dexlansoprazole for this indication.
- The product showed clear superiority over placebo and a labeling claim to this effect is acceptable.
- The product showed strong superiority over placebo for the key secondary endpoint "percentage of days without (b) (4) heartburn." Claims to this effect could be presented in labeling if the Biostatistics reviewers agree that the sponsor's hierarchical plan for assessing these secondary endpoints is sound.
- The language (b) (4) s" is based on exploratory endpoints and should not be permitted in the indication.
- The language (b) (4) s" is not clinically appropriate for use in the indication given the current understanding of (b) (4) GERD (see Section 6.3.9). However, the clinical study results could be presented in an appropriate section of the label (i.e., Clinical Studies) to provide more detailed information regarding the design of the study and the analysis of the primary endpoint.
- The indication should be reworded to "treatment of heartburn associated with non-erosive GERD."

## 1.2 Risk Benefit Assessment

Since this review evaluated only the efficacy of the product, it is difficult to provide a detailed risk/benefit assessment here. However, the reviewer is aware of several safety concerns that have arisen with this application (see Dr. Tamara Johnson's review of safety). Although dexlansoprazole is effective for all 3 indications being sought, the reviewer strongly believes that no convincing evidence of additional benefit over existing therapies has been demonstrated in the current application.

Due to this lack of additional benefit along with the safety concerns that have been voiced in Dr. Johnson's review, the reviewer believes that the benefit/risk profile for dexlansoprazole is unfavorable at this time, and that future studies should be required to clarify the nature of the potential safety signal before any approval for marketing is granted.

Clinical Review  
Keith B. St. Amand, MD  
NDA 22-287  
(b) (4) (dexlansoprazole)

### 1.3 Recommendations for Postmarketing Risk Management Activities

N/A

### 1.4 Recommendations for other Post Marketing Study Commitments

N/A

## 2 Introduction and Regulatory Background

### 2.1 Product Information

**Product name:** Dexlansoprazole (hereafter abbreviated as dex)

**Proposed Trade name:** (b) (4) (b)

**Proposed Indications:**

1. Healing (b) (4) of all grades of erosive esophagitis
2. Maintenance of healing of erosive esophagitis (b) (4)
3. Treatment of (b) (4) heartburn (b) (4) s associated with gastroesophageal reflux disease (GERD)

**Proposed Age Group:** Adults

**Pharmacologic Class:** Proton pump inhibitor (PPI)

**Route of Administration, Description, and Formulation:**

Dex is supplied as a dual delayed-release formulation in capsules for oral administration. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles. One type of granule is designed to release dexlansoprazole after the granules reach the proximal small intestine; the second type of granule is designed to release dexlansoprazole in the distal region of the small intestine, generally several hours later.

Dex is available in (b) dosage strengths: 30 mg, 60 mg, (b) (4) mg per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole (active ingredient) and the following inactive ingredients: sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymer, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide.

Clinical Review  
Keith B. St. Amand, MD  
NDA 22-287

(b) (4) (dexlansoprazole)

**Proposed Treatment Regimens:**

Healing of EE: 60 mg (b) (4) once daily for up to 8 weeks

Maintenance of Healed EE: 30 mg (b) (4) once daily for up to 6 months

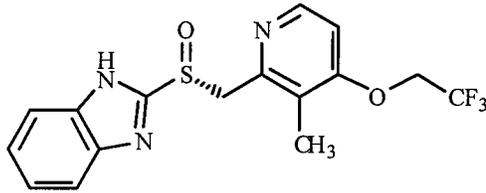
Symptomatic GERD: 30 mg once daily for 4 weeks

**Molecular Formula:**

The active ingredient in (b) (4) (dexlansoprazole) Delayed Release Capsules is (+)-2-[(R)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl} sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Dexlansoprazole is the R-enantiomer of lansoprazole (a racemic mixture of the R- and S-enantiomers).

Its empirical formula is: C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S, with a molecular weight of 369.36.

The structural formula is:



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(b) (4) (dexlansoprazole)

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Gastroesophageal reflux disease (GERD) comprises a spectrum of acid-related disorders, including nonerosive GERD and erosive esophagitis (EE). Nonerosive GERD is defined as the presence of symptoms caused by intraesophageal acid reflux in patients with absence of endoscopically observed injury to the esophageal mucosa.<sup>1</sup> Erosive esophagitis is defined as the presence of superficial esophageal erosions in patients with or without typical GERD symptoms.

Erosive esophagitis is diagnosed during endoscopy in up to 50% of patients with GERD symptoms.<sup>2</sup> The severity of these symptoms is associated with the extent and duration of gastric acid exposure in the esophagus.<sup>3,4</sup> Patients who do not receive treatment, or in whom acid reflux is not effectively controlled, are at risk of developing significant complications, such as bleeding, strictures, and the premalignant condition of Barrett's esophagus.<sup>5,6</sup>

Therapy for GERD is largely focused on the prevention of reflux of gastric acid into the esophagus, either by pharmacological or surgical means, with surgery usually reserved for intractable cases. Pharmacological management of GERD includes treatment with antacids, histamine<sub>2</sub>-receptor antagonists, prokinetic agents, and proton pump inhibitors (PPIs). PPIs, which are labeled for once daily (QD) dosing, are the most effective medications for relieving GERD symptoms, healing the injured mucosa, maintaining a healed mucosa, and preventing the development of complications.<sup>7</sup>

Multiple PPIs are currently available for both the healing and maintenance of erosive esophagitis and for treating heartburn associated with non-erosive GERD.

***Appears This Way On Original***

Clinical Review  
 Keith B. St. Amand, MD  
 NDA 22-287

(b) (4) (dexlansoprazole)

**Table 1: Currently Available Proton Pump Inhibitors for Proposed Indications**

<b>Drug Name</b>	<b>Trade Name</b>	<b>Sponsor</b>	<b>Indications/Doses</b>	<b>Date of Approval</b>
Omeprazole	Prilosec™	Astra Zeneca	HEE: 20 mg QD MHEE: 20 mg QD sGERD: 20 mg QD	14 Sep 1989
Lansoprazole	Prevacid™	TAP	HEE: 30 mg QD MHEE: 15 mg QD sGERD: 15 mg QD	10 May 1995
Rabeprazole	Aciphex™	Eisai	HEE: 20 mg QD MHEE: 20 mg QD sGERD: 20 mg QD	19 Aug 1999
Pantoprazole	Protonix™	Wyeth	HEE: 40 mg QD MHEE: 40 mg QD sGERD: not approved	2 Feb 2000
Esomeprazole	Nexium™	Astra Zeneca	HEE: 20/40 mg QD MHEE: 20 mg QD sGERD: 20 mg QD	20 Feb 2001
Omeprazole/sodium bicarbonate	Zegerid™	Santarus	HEE: 20 mg QD MHEE: not approved sGERD: 20 mg QD	15 Jun 2004

*Source: Package Inserts for each product; Drugs@FDA website*

***Appears This Way On Original***

(b) (4) (dexlansoprazole)

Additional less potent therapies that have been approved for the proposed indications include the following products in the table below. Most if not all of these products are now considered alternative or adjunctive rather than primary therapeutic options for the proposed indications.

**Table 2: Non-PPI Approved Therapies for Proposed Indications**

Drug Name	Trade Name	Sponsor	Indications/Doses	Date of Approval
Ranitidine	Zantac™	GSK	HEE: 150 mg QID MHEE: 150 mg BID sGERD: 150 mg BID	9 Jun 1983
Nizatidine	Axid™	GSK	HEE: 150 mg BID MHEE: not approved sGERD: 150 mg BID	12 Apr 1988
Famotidine	Pepcid™	Merck	HEE: 20/40 mg BID MHEE: not approved sGERD: 20 mg BID	15 Oct 1986
Cimetidine	Tagamet™	GSK	HEE: not approved MHEE: not approved sGERD: 800 mg BID/400 mg QID	16 Aug 1977
Metoclopramide	Reglan™	Schwarz	HEE: 15 mg QID MHEE: not approved sGERD: 10/15 mg QID	30 Dec 1980

Source: Package Inserts for each product; Drugs@FDA website

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

Lansoprazole, a PPI which was approved in the US in 1995, has been marketed for over 12 years, is widely prescribed and has a well-established safety profile. Lansoprazole has a chiral center at the asymmetric sulfinyl group and, therefore, has 2 enantiomers: R- and S-lansoprazole, known as dexlansoprazole (or TAK-390) and T-168391, respectively. *In vitro* studies have shown that dexlansoprazole, S-lansoprazole, and lansoprazole suppress gastric acid secretion to the same extent, by specific inhibition of the (H<sup>+</sup>,K<sup>+</sup>)-ATPase enzyme system (proton pump) at the surface of the gastric parietal cell. However, an equivalent dose of S-lansoprazole exhibits a lower *in vivo* pharmacological response. The diminished pharmacodynamic (PD) effect of S-lansoprazole is due to its rapid clearance compared to dexlansoprazole *in vivo*. After oral administration of lansoprazole, dexlansoprazole is the predominant circulating enantiomer, representing approximately 85% of the area under the plasma concentration-time curve (AUC). Racemic conversion of dexlansoprazole to S-lansoprazole does not occur in humans, as no S-lansoprazole is detectable in plasma following oral administration of dexlansoprazole. Thus, the majority of the treatment effect following dosing of lansoprazole is attributable to the R-enantiomer, supporting the selection of dexlansoprazole as the enantiomer for development.

Clinical Review  
Keith B. St. Amand, MD  
NDA 22-287

**(b) (4)** (dexlansoprazole)

## 2.4 Important Safety Issues With Consideration to Related Drugs

See Dr. Tamara Johnson's safety review.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The table below summarizes the presubmission regulatory activity related to this NDA.

**Table 3: Presubmission Regulatory Activity for NDA 22-287**

Meeting Date	Type of Meeting/Purpose
6 Oct 2004	Type C/Development Plan
12 May 2005	Type B/End-of-Phase 2
1 Mar 2006	Type C/Phase 3 Program
22 Jun 2006*	Type B/End-of-Phase 2, CMC
23 Aug 2007	Type B/Pre-NDA CMC
1 Oct 2007	Type B/Pre-NDA Clinical, Nonclinical, and Regulatory
2 Nov 2007	Type C/Pediatric Assessment Plan

## 2.6 Other Relevant Background Information

N/A

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### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

Three sites were selected for Division of Scientific Investigations (DSI) inspection for this application. While some minor violations were noted, the final assessment was that the data from all three sites were valid and could be used in support of the NDA. Please see Dr. Khairy Malek's full review for more details.

#### **3.2 Compliance with Good Clinical Practices**

All of the pivotal studies were conducted in accordance with the clinical protocol, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP) guidelines, US Food and Drug Administration (FDA) GCP regulations, the ethical principles stated in the Declaration of Helsinki, and all applicable local regulations. The studies did not begin until all of the requirements of the appropriate regulatory authorities were fulfilled. The investigators assured that the studies were conducted in accordance with the provisions as stated in the FDA regulations and in compliance with prevailing local laws and customs.

#### **3.3 Financial Disclosures**

The sponsor certified that there were no financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. Each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in dexlansoprazole or a significant equity in the sponsor; no investigators disclosed any such interests.

***Appears This Way On Original***

(b) (4) (dexlansoprazole)

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

### 4.1 Chemistry Manufacturing and Controls

There were no significant regulatory issues raised by the CMC reviewer at the time of the completion of the clinical efficacy review.

### 4.2 Preclinical Pharmacology/Toxicology

From a preclinical standpoint, approval of dexlansoprazole was recommended by the Pharm/Tox reviewer for the proposed indications.

However, the reviewer (Dr. Ke Zhang) recommended the following nonclinical studies be performed post-approval:

(1) *in vitro* studies on the contractile responses in the isolated coronary arteries from dogs or monkeys and (2) *in vivo* studies in cardiac ischemic animal models.

According to the reviewer, the major target organ of toxicity was the stomach identified in the 3-month repeat-dose toxicity study in rats and dogs. The results indicated that both dexlansoprazole and lansoprazole have similar toxicity profiles. Dexlansoprazole was not teratogenic in the segment II reproductive toxicity study in rabbits. Dexlansoprazole was positive in the Ames tests and in the *in vitro* chromosome aberration test using Chinese hamster lung cells.

In addition, the following changes to the proposed labeling were recommended.

#### 8.1 Pregnancy Pregnancy Category B.

(b) (4)



Teratology studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (16 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

(b) (4) (dexlansoprazole)

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dexlansoprazole was positive in the Ames test and in the in vitro chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the in vivo mouse micronucleus test.

## 4.3 Clinical Pharmacology

To further enhance the potential for dexlansoprazole to demonstrate clinical benefit, especially in treating patients with unmet medical needs, the sponsor developed a dual delayed release formulation of dexlansoprazole, referred to as dexlansoprazole modified release (MR). This novel formulation consists of 2 types of granules contained within a single capsule. Each type of granule has a different pH-dependent release profile. Approximately 25% of the drug is released within 1 to 2 hours of administration, followed by a second release phase for the remaining 75% of the dose within 4 to 5 hours. This dual delayed release formulation is designed to extend the duration of drug exposure and maintain pharmacologically active levels of drug over a longer time period. As a result, the pharmacokinetic (PK) profile of dexlansoprazole following the administration of dexlansoprazole MR is characterized by a concentration-time profile with 2 distinct peaks. In order to achieve this 2-peak, prolonged PK profile, dexlansoprazole MR releases drug substance over a longer period of time, thus requiring higher daily doses and consequently higher AUCs, without a commensurate increase in maximum plasma drug concentration (C<sub>max</sub>), compared to that following administration of the conventional lansoprazole delayed-release formulation.

The following comments were provided by the Clinical Pharmacology reviewer, Dr. Jane Bai.

--The application is acceptable from the clinical pharmacology perspective provided the labeling comments are adequately addressed by the sponsor. Regarding the proposed doses for individual indications, the (b) (4) QD regimens did not provide additional benefits in healing erosive esophagitis (EE) and in maintenance of healed EE, respectively, than the respective (b) (4) dose regimens of 60 mg and 30 mg. Therefore, if the safety profiles of the drug are acceptable to the Division of Gastroenterology Products, our recommended dosing regimens for the proposed indications are as listed below.

Indication	Recommended dose	Frequency
Healing EE	60 mg	Once daily for up to 8 weeks
Maintenance of Healed EE	30 mg	Once daily*
Symptomatic GERD	30 mg	Once daily for up to 8 weeks

\*Controlled studies did not extend beyond 6 months. gastroesophageal reflux disease: GERD

--The percentage of time intragastric pH was >4 over the 24 hour dosing interval was 57% when dexlansoprazole was administered after food compared to 64% in the fasting group (and 62-66% when dexlansoprazole was administered before food). The clinical significance of this finding is

Clinical Review  
Keith B. St. Amand, MD  
NDA 22-287

(b) (4) (dexlansoprazole)

not known especially after multiple dosing. Since in all clinical trials, dexlansoprazole was administered before breakfast, this will be reflected in the label.

--There was no significant difference in dexlansoprazole exposure when administered as an intact capsule or as granules sprinkled over applesauce.

--A single 25mg dose of warfarin, another CYP2C9 substrate, was administered following 6 doses of dexlansoprazole 90mg. No significant interaction was observed based on the AUC,  $C_{max}$ , of R- and S-warfarin,  $INR_{max}$ , and  $INR_{144}$ . [However, the label will have a caution statement as the study may not predict the outcome in patients.]

--The differences in the pharmacokinetics of dexlansoprazole between healthy subjects and patients with moderate hepatic impairment reached statistical significance for  $C_{max,u}$ ,  $AUC_t$ ,  $AUC_{\infty}$ , and  $AUC_{\infty,u}$  (Mean  $C_{max}$  in moderate hepatic impairment patients increased 44% and  $AUC$  116%.) Dose reduction in patients with hepatic impairment is recommended. The sponsor did not conduct a study in patients with severe hepatic impairment. Further dose reduction in these patients or alternative treatments should be considered.

--The QT/IRT review team concluded that "No significant QT prolongation effect of (b) (4) (90 mg and 300 mg) was detected in this TQT study."

## 5 Sources of Clinical Data

### 5.1 Tables of Clinical Studies

The sponsor for NDA 22-287 is seeking 3 separate indications for dexlansoprazole. This section will not discuss individual indications but will simply list all studies that have been submitted in support of the application.

***Appears This Way On Original***

(b) (3)(d) (dexlansoprazole)

The first group of tables presented below lists the biopharmaceutics studies (bioavailability, bioequivalence, etc.) that comprise the NDA.

**Table 4: Listing of Biopharmaceutic Studies for NDA 22-287**

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
BA	I-P104-069	To compare the effect of several feeding conditions on the PK of a single 90 mg oral dose dexlansoprazole MR and to evaluate the safety of dexlansoprazole MR after administration of a single 90 mg oral dose to healthy subjects in fed and fasted states	Randomized, open-label, 4-period crossover  NA	Single oral doses of dexlansoprazole MR 90 mg under fed and fasting conditions	14/14	Healthy Subjects	4 single doses separated by a 5-day washout	Complete Full
BA	I-P106-146	To evaluate the timing of food on the PD and PK of dexlansoprazole following a single oral dose of 90 mg dexlansoprazole MR.	Randomized, open-label, 4-period crossover  Placebo	Single oral doses of dexlansoprazole MR 90 mg or placebo under fed and fasting conditions in each period	29/19	Healthy Subjects	4 single doses separated by a 5-day washout	Complete Full
BA/BE	I-P106-148	To evaluate relative bioavailability and assess bioequivalence of dexlansoprazole following administration of a 90 mg single oral dose of dexlansoprazole MR granules administered sprinkled over applesauce relative to an intact capsule administered orally	Randomized, open-label, 2-period crossover  NA	Single oral doses of dexlansoprazole MR 90 mg administered as granules from a single capsule sprinkled over applesauce or as an intact capsule	48/12	Healthy Subjects	2 single doses separated by a 5-day washout	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

**Appears This Way On Original**

(b) (4) (d) (dexlansoprazole)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
BA/BE	T-P106-149	To evaluate the bioavailability, PK, and safety of dexlansoprazole after administration of 90 mg single oral doses of 3 dexlansoprazole MR formulations	Randomized, open-label, 3-period crossover NA	Single oral doses of dexlansoprazole MR 90 mg with 25%, 45%, or 30% coatings	30/30	Healthy Subjects	3 single doses separated by a 5-day washout	Complete Full
PK	T-P105-141	To assess the absorption, distribution, metabolism, and excretion of dexlansoprazole in healthy subjects on Day 5 after administration of dexlansoprazole MR 60 mg QD for 4 days followed by a single 60 mg equivalent oral dose of [ <sup>14</sup> C] dexlansoprazole containing approximately 100 µCi of radioactivity on Day 5	Open-label NA	Oral dexlansoprazole MR 60 mg QD for 4 days followed by a single 60 mg oral equivalent dose of [ <sup>14</sup> C] on Day 5 under fasting conditions	6/0	Healthy Male Subjects	3 days	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	RCP-003	To characterize the preliminary PK profiles of 4 new formulations of dexlansoprazole (MR-A to MR-D) when administered as single oral dose of 2 capsules, each containing 30 mg dexlansoprazole	Open-label, single-dose, parallel NA	Single oral doses of dexlansoprazole MR-A, dexlansoprazole MR-B, dexlansoprazole MR-C, or dexlansoprazole MR-D 60 mg under fasting conditions	32/0	Healthy Male Subjects	Single dose	Complete Full
PK	T-P105-129	To evaluate the PK and safety of dexlansoprazole MR in subjects with symptomatic nonerosive GERD receiving multiple doses of dexlansoprazole MR 30 mg, 60 mg, or 90 mg QD for 8 days	Randomized, open-label, parallel-group NA	Multiple oral doses of dexlansoprazole MR: 30 mg, 60 mg, or 90 mg	10/26	Subjects with Symptomatic Nonerosive GERD	8 days	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

(b) (4) (d) (dexlansoprazole)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	T-P105-115	To evaluate the safety and PK of a single oral dose of dexlansoprazole MR (60 mg) when administered to subjects with moderate chronic hepatic impairment and subjects with normal hepatic function	Open-label, parallel-group NA	Single oral dose of dexlansoprazole MR 60 mg	12/12	Healthy and Hepatically Impaired Subjects	Single dose	Complete Full
PK	T-P105-119	To assess the effect of age and gender on the PK of a single oral dose of dexlansoprazole MR 60 mg and to evaluate the safety following a single oral dose of dexlansoprazole MR 60 mg in young and elderly healthy subjects	Open-label, parallel-group NA	Single oral dose of dexlansoprazole MR 60 mg	12/12	Healthy Subjects	Single dose	Complete Full
PK/PD	T-P105-132	To evaluate the effect of multiple QD doses of dexlansoprazole MR 90 mg on the PK and PD of a single warfarin 25 mg dose	Randomized, double-blind, placebo-controlled, 2-period crossover with open-label warfarin Placebo	Oral dexlansoprazole MR 90 mg QD or placebo QD for 11 days; oral warfarin 25 mg coadministered on Day 6 of each period	19/0	Healthy Subjects	Two 11-day periods separated by a 10-day washout	Complete Full

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 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

**Appears This Way On Original**

(b) (4) (d)(dexlansoprazole)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	T-P105-133	To evaluate the effect of multiple QD doses of 90 mg dexlansoprazole MR on the PK of a single oral dose of 250 mg phenytoin	Randomized, double-blind, placebo-controlled, 2-period crossover, with open-label phenytoin Placebo	Oral dexlansoprazole MR 90 mg QD for 9 days or placebo QD for 9 days; phenytoin 10 mL oral suspension coadministered on Day 6 of each period	14/2	Healthy Subjects	Two 9-day periods separated by a 7-day washout	Complete Full
PK	T-P105-134	To evaluate the effect of multiple QD doses of dexlansoprazole MR 90 mg on the PK of a single oral dose of diazepam 5 mg	Randomized, double-blind, placebo-controlled, 2-period crossover with open-label diazepam Placebo	Oral dexlansoprazole MR 90 mg QD for 11 days or placebo QD for 11 days; oral diazepam 5 mg coadministered on Day 6 of each period	13/7	Healthy Subjects	Two 11-day periods separated by a 7-day washout	Complete Full
PK	T-P105-139	To evaluate the effect of multiple QD doses of dexlansoprazole MR 90 mg on the PK of theophylline following a single IV dose of aminophylline	Randomized, double-blind, placebo-controlled, 2-period crossover with open-label aminophylline Placebo	Oral dexlansoprazole MR 90 mg QD or placebo QD for 9 days; aminophylline dehydrate 400 mg IV coadministered on Day 8 of each period	8/12	Healthy Subjects	Two 9-day periods separated by a 10-day washout	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK/PD	M01-309	To compare the PD of the R+ enantiomer and S- enantiomer of lansoprazole to racemate lansoprazole, and to compare the PK profiles of the test R+ enantiomer and S- enantiomer, when dosed separately, to the reference racemate lansoprazole and to summarize the safety profile for each study medication	Randomized, open-label, crossover Active	Oral dexlansoprazole 30 mg, oral dexlansoprazole 20 mg, oral S-lansoprazole 30 mg, oral lansoprazole 30 mg QD for 5 day	23/14	Healthy Subjects	Four 5-day periods separated by ≥7-day washout	Complete Full
PK/PD	C02-004	To compare the PD (gastric pH measurement) of 60 mg and 90 mg doses of dexlansoprazole with those of reference doses of esomeprazole 40 mg and lansoprazole 30 mg and to assess the PK and safety of each regimen	Randomized, open-label, crossover Active	Oral dexlansoprazole 60 mg, oral dexlansoprazole 90 mg, oral esomeprazole 40 mg, or oral lansoprazole 30 mg QD for 5 days	17/15	Healthy Subjects	Four 5-day periods separated by ≥7-day washout	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
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Clinical Review  
 Keith B. St. Amand, MD  
 NDA 22-287  
 (b) (4) (dexlansoprazole)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK/PD	T-P104-092	To identify any potential effects of dexlansoprazole MR on QT/QTc interval and safety at single doses up to 300 mg, as compared to placebo, in healthy subjects and to compare the PK profiles of single doses of 90 mg and 300 mg of dexlansoprazole MR to active comparator Avelox in the same subjects	Randomized, double-blind, 4-period crossover  Placebo and Active	Single oral doses of dexlansoprazole MR 90 and 300 mg, placebo for dexlansoprazole MR, or oral Avelox 400 mg	33/7	Healthy Subjects	4 single doses separated by a 5-day washout	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK/PD	T-P104-100	To characterize the plasma gastrin concentration profile on Day 1 and Day 5 following QD oral administration of 90 mg or 120 mg of dexlansoprazole MR or 30 mg of lansoprazole delayed-release capsules for 5 consecutive days, to evaluate the relationship between the plasma gastrin profile and the PK of 90 mg or 120 mg of dexlansoprazole MR or 30 mg of lansoprazole on Day 1 and Day 5, and to assess the safety of 90 mg and 120 mg of dexlansoprazole MR and 30 mg of lansoprazole following QD oral administration for 5 consecutive days to healthy subjects	Randomized, open-label, 3-period crossover  Active	Single oral doses of dexlansoprazole MR 90 and 120 mg and oral lansoprazole 30 mg QD for 5 consecutive days	36/6	Healthy Subjects	Four 5-day periods separated by a 14-day washout	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

(b) (4) (d) (dexlansoprazole)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK/PD	CPH-501	To evaluate the PD and PK profiles and the effect of timing of a meal of the newly developed oral capsule formulation of dexlansoprazole compared to Nexium (40 mg esomeprazole) in healthy males subjects	Randomized, open-label, 4-period crossover  Active	Oral dexlansoprazole MR capsule-1 90 mg or oral Nexium (40 mg esomeprazole) QD for 5 days under fasted conditions	24/0	Healthy Male Subjects	Four 5-day periods separated by $\geq 7$ -day washout	Complete Full
PK/PD	CPH-502	To evaluate the PD and PK profiles of dexlansoprazole MR capsule-3, when administered as multiple oral doses (90 mg) compared to Nexium (40 mg esomeprazole)	Randomized, open-label, 2-period crossover  Active	Oral dexlansoprazole MR capsule-3 90 mg or oral Nexium (40 mg esomeprazole) QD for 5 days under fasted conditions	24/0	Healthy Male Subjects	Two 5-day periods separated by $\geq 7$ -day washout	Complete Full
PK/PD	CPH-503	To evaluate the PD and PK profile of dexlansoprazole, capsule-IMP-3 compared to dexlansoprazole MR capsule-3 and Nexium (40 mg esomeprazole) as references	Randomized, open-label, 3-period crossover  Active	Oral dexlansoprazole MR capsule-IMP-3 90 mg, oral dexlansoprazole MR capsule-3 90 mg, or oral Nexium (40 mg esomeprazole) QD for 5 days under fasted conditions	24/0	Healthy Male Subjects	Three 5-day periods separated by $\geq 7$ -day washout	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK/PD	RCP-0022	To evaluate the PK and PD profile of a newly developed capsule formulation of dexlansoprazole 60 mg when administered as multiple oral doses compared to Nexium (40 mg esomeprazole) as reference	Randomized, open-label, 2-period crossover  Active	Oral dexlansoprazole MR-BB 60 mg for 5 days under fasted conditions or oral Nexium (40 mg esomeprazole) QD for 5 days under fasted conditions	24/0	Healthy Male Subjects	Two 5-day periods separated by $\geq 7$ -day washout	Complete Full
PK/PD	RCP-0023	To evaluate the PK and PD profile of a newly developed capsule formulation of dexlansoprazole 90 mg when administered as multiple oral doses compared to Nexium (40 mg esomeprazole) as reference	Randomized, open-label, multiple-dose, 2-period crossover  Active	Oral dexlansoprazole MR-E 90 mg or oral Nexium (40 mg esomeprazole) QD for 5 days under fasted conditions	24/0	Healthy Male Subjects	Two 5-day periods separated by $\geq 7$ -day washout	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

Source of above tables: Table 5.2.a., Module 5.2, NDA 22-287

(b) (4) (d) (dexlansoprazole)

The following group of tables presents the studies that were performed to evaluate the efficacy and/or safety of dexlansoprazole. The first 6 studies are considered pivotal efficacy studies for the current NDA submission.

**Table 5: Listing of Clinical Studies for NDA 22-287**

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Efficacy and Safety	T-GD04-082	To assess the efficacy in relief of daytime and nighttime heartburn over 4 weeks as assessed by daily electronic diary of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to placebo in subjects with symptomatic, nonerosive GERD; to assess the safety of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to placebo in subjects with symptomatic, nonerosive GERD. The secondary objective was to assess the efficacy of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to placebo in relief of nighttime heartburn over 4 weeks as assessed by daily electronic diary	Randomized, double-blind, multicenter, placebo-controlled, parallel-group, 3-arm  Placebo	60 mg oral dexlansoprazole MR QD or 90 mg oral dexlansoprazole MR QD or oral placebo QD	265/643	Subjects with Symptomatic Nonerosive GERD	4 weeks	Complete Full

BA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

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**(b) (4)** dexlansoprazole

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Efficacy and Safety	T-GD05-137	To assess the efficacy in relief of daytime and nighttime heartburn over 4 weeks as assessed by daily electronic diary of dexlansoprazole MR (30 mg QD and 60 mg QD) compared to placebo in subjects with symptomatic, nonerosive GERD; to assess the safety of dexlansoprazole MR (30 mg QD and 60 mg QD) compared to placebo in subjects with symptomatic, nonerosive GERD. The secondary objective was to assess the efficacy of dexlansoprazole MR (30 mg QD and 60 mg QD) compared to placebo in relief of nighttime heartburn over 4 weeks as assessed by daily electronic diary	Randomized, double-blind, multicenter, placebo-controlled, parallel-group, 3-arm  Placebo	30 mg oral dexlansoprazole MR QD or 60 mg oral dexlansoprazole MR QD or oral placebo QD	274/673	Subjects with Symptomatic Nonerosive GERD	4 weeks	Complete Full

BA=bioavailability; BE=bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD=once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Efficacy and Safety	T-EE04-084	To assess the efficacy and safety in healing EE over 8 weeks of dexlansoprazole MR (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 MR (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	Randomized, double-blind, active-controlled  Active	60 mg oral dexlansoprazole MR QD or 90 mg oral dexlansoprazole MR QD or 30 mg oral lansoprazole delayed release QD	1111/927	Subjects with EE	4 or 8 week	Complete Full

BA=bioavailability; BE=bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD=once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

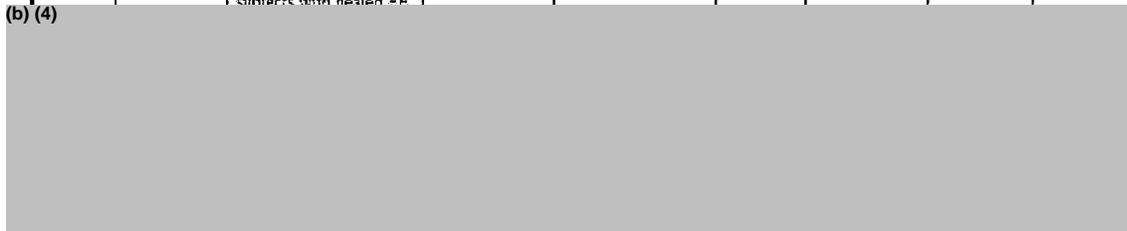


Clinical Review  
 Keith B. St. Amand, MD  
 NDA 22-287

(b) (4) dexlansoprazole)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type	Study and Control Drugs, Dose, Route and Regimen	Number of Subjects (M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Efficacy and Safety	T-EE03-133	To assess the efficacy in maintenance of healing and safety of dexlansoprazole MR (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 MR (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	Randomized, double-blind, placebo-controlled  Placebo	30 mg oral dexlansoprazole MR QD or 60 mg oral dexlansoprazole MR QD or oral placebo QD	213/230	Subjects with Healed EE	6 Months	Complete Full

(b) (4)



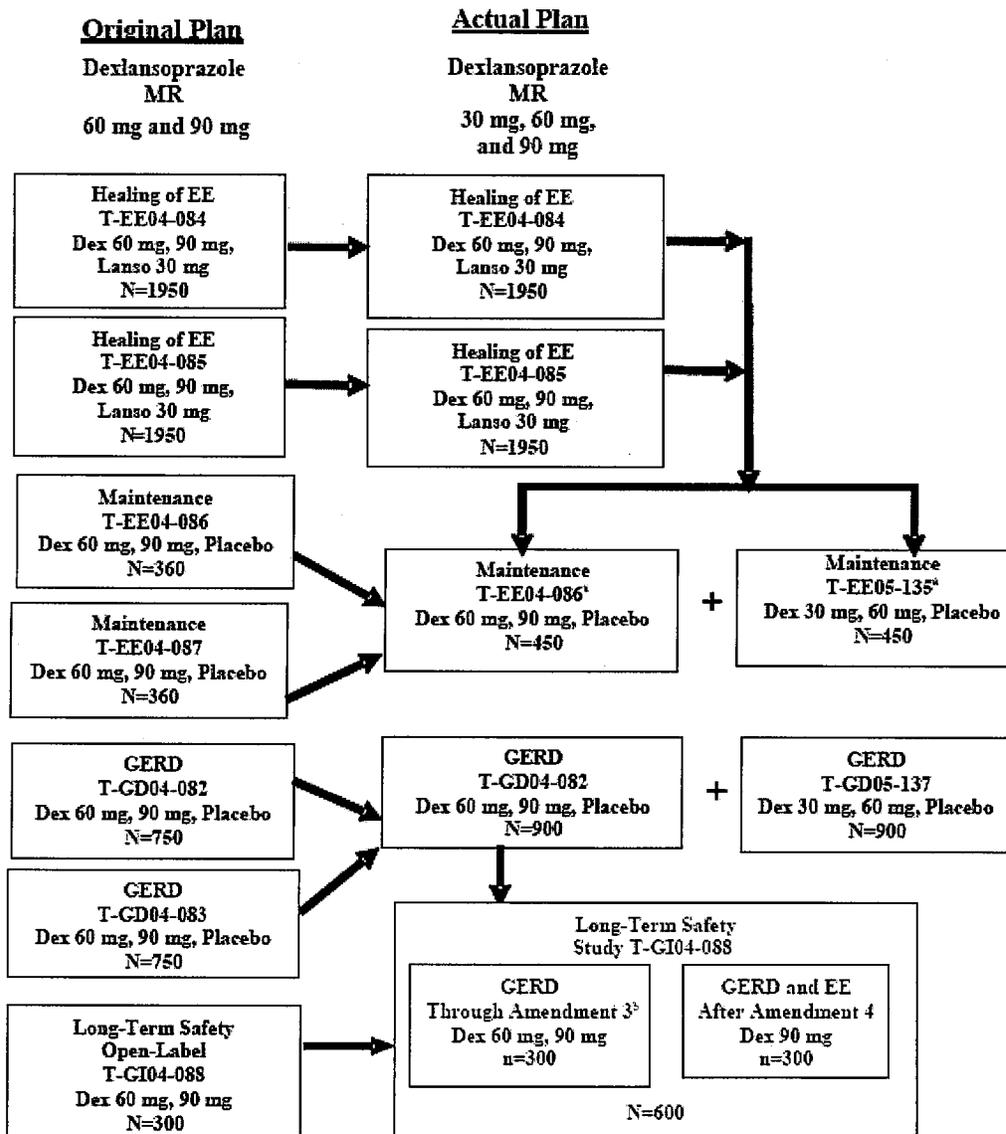
AA=bioavailability; BE=Bioequivalence; EE=erosive esophagitis; F=female; GERD=gastroesophageal reflux disease; IV=intravenous; M=male; MR=modified release; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic; QD = once daily; QOL=quality of life  
 a Total number of subjects enrolled under Amendments 1 to 4, inclusive, to date

Source of above tables: Table 5.2.a., Module 5.2, NDA 22-287

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The following flowchart reiterates the pivotal efficacy studies and the long-term safety study and illustrates the history of the development plan for dexlansoprazole.

Figure 1: Development Plan for NDA 22-287



Dex=dexlansoprazole MR; Lanso=lansoprazole 30 mg QD.

a Subjects in Studies T-EE04-086 and T-EE05-135 rolled over from either Study T-EE04-084 or T-EE04-085.

b These subjects in Study T-GI04-088 rolled over from Study T-GD04-082.

Source: Figure 2.5.a., p.13, Module 2.5, NDA 22-287

Clinical Review  
Keith B. St. Amand, MD  
NDA 22-287  
**(b) (4)** (dexlansoprazole)

**Medical Officer Comments:**

**The consolidation of studies as depicted in the flowchart above was prospectively defined and approved by the agency in discussions with the sponsor.**

## 5.2 Review Strategy

Due to the large number of clinical studies submitted for this application, the clinical review will be conducted by two medical officers. This reviewer will be performing the efficacy review of the six pivotal studies, while Dr. Tamara Johnson will be performing the safety review for all studies. For this reason, certain sections of this review will contain the following instruction: "Please see Dr. Tamara Johnson's review for this section."

## 5.3 Discussion of Individual Studies

Further discussion of individual studies will be undertaken (when necessary) in the respective efficacy, safety, and biopharm reviews.

## 6 Review of Efficacy

Note: The current application seeks 3 new indications for dexlansoprazole. The reviewer will first present a summary of the efficacy findings for each indication. Following that, each indication will be analyzed and discussed as follows:

- Section 6.1: Healing **(b) (4)** of all grades of erosive esophagitis (HEE)
- Section 6.2: Maintenance of healing of erosive esophagitis **(b) (4)** (MHEE)
- Section 6.3: Treatment of **(b) (4)** heartburn **(b) (4)** associated with gastroesophageal reflux disease (sGERD)

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## Efficacy Summary

The following is a summary of the efficacy findings of the pivotal studies performed in support of each proposed indication. Rather than duplicating them here, any recommendations for regulatory action related to these findings are presented in Section 1.1.

### Healing of Erosive Esophagitis:

- In each of the two HEE studies, dexlansoprazole 60 mg and 90 mg daily were both non-inferior to lansoprazole 30 mg daily for the primary endpoint, “the percentage of subjects who had complete healing of EE over 8 weeks as assessed by endoscopy.”
- In addition, dexlansoprazole 90 mg daily was statistically superior to lansoprazole 30 mg daily in both individual studies and in the integrated analysis, with a maximum therapeutic gain of **(b) (4)**. The 60 mg dose of dexlansoprazole was statistically superior to lansoprazole 30 mg daily for one individual study and in the integrated analysis, with a maximum therapeutic gain of 6.3%.
- Subgroup analyses for the primary endpoint supported the findings seen in the patient population as a whole.
- For the key secondary endpoint “Week 8 healing for baseline LA Grades C or D,” dex 90 mg demonstrated a statistically significant gain of **(b) (4)** over lansoprazole 30 mg in the integrated analysis, but no differences were seen in either of the individual studies.
- For the same endpoint, dex 60 mg demonstrated a statistically significant gain of 15% over lansoprazole 30 mg in one individual study but failed to show a difference in either the second study or in the integrated analysis.
- Neither dose of dex showed a statistically significant gain over lansoprazole 30 mg for the key secondary endpoint “healing at Week 4” in either of the individual studies.
- No significant differences were seen between the two dex doses for the primary or key secondary endpoints.

### Maintenance of healing of erosive esophagitis:

- All dex doses (30 mg, 60 mg, and 90 mg daily) were statistically superior to placebo for the primary endpoint “percentage of subjects who maintained healed EE for 6 months as assessed by endoscopy.”
- Dex 60 mg demonstrated therapeutic gains over dex 30 mg in subjects with more severe grades of EE prior to healing and in subjects who took longer to heal, but these gains were not statistically significant, possibly due to the low numbers of patients in the subgroups.

**(b) (4)** (dexlansoprazole)

- No additional clinical benefit was seen in patients on dex 90 mg (vs. 60 mg).
- Significant differences were seen between all doses of dex and placebo for both key secondary endpoints (“percentage of 24-hr heartburn-free days” and “percentage of days without nighttime heartburn”).

#### Treatment of heartburn in non-erosive GERD:

- All 3 doses of dex (30 mg, 60 mg, and 90 mg daily) showed strong statistical superiority over placebo for the primary endpoint “percentage of days with neither daytime nor nighttime heartburn.”
- Subgroup analyses for the primary endpoint confirmed the findings seen in the overall population.
- All 3 doses of dex showed strong statistical superiority over placebo for the key secondary endpoint “percentage of days without nighttime heartburn.”
- No significant differences were seen between any two dex doses.

### **6.1 Healing of Erosive Esophagitis (HEE)**

The first proposed indication to be reviewed is “healing **(b) (4)** of all grades of erosive esophagitis.” The sponsor is seeking approval for **(b) (4)**. Since the two studies performed for this indication are identical in design and dosing, the focus of the review will be on the integrated analysis of the data. Where necessary, individual study results will be presented and discussed further.

#### 6.1.1 Methods

##### 6.1.1.1 Overview of Study Design

Studies T-EE04-084 and T-EE04-085 were both Phase 3, randomized, double-blind, active-controlled, multicenter, 3-arm studies with up to 8-week treatment periods. The studies were designed to evaluate healing of EE and relief of GERD-related symptoms (i.e., heartburn, acid regurgitation, dysphagia, belching, and epigastric pain) and compared the efficacy and safety of dexlansoprazole MR 60 mg QD and 90 mg QD with that of delayed-release lansoprazole 30 mg QD. Lansoprazole 30 mg QD was chosen because it is the approved dose for healing of EE.

The figure below provides a graphical depiction of the studies and their relationship to the MHEE studies that followed.



(b) (3)(d) (dexlansoprazole)

The following table presents more detailed information regarding number and location of study sites, study objectives and endpoints, and number of subjects by arm. (More detailed discussion of endpoints will follow later in this section.)

**Table 6: Description of Controlled Clinical Efficacy Studies for HEE**

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>b</sup>						
						Study and Control Drugs Dose, Route, Regimen	Subjects by Arm Entered/ Completed	Gender M/F	Median Age (Range)	Duration of Treatment	Study Population and Primary Inclusion Criteria
I-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 Dec-05/Jan-07	150 2038/1950	Randomized, double-blind, active-controlled  Active	To assess the efficacy and safety in healing EE over 8 weeks of dexlansoprazole MR (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 MR (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, fasting gastrin levels, and vital signs.						
						60 mg oral dexlansoprazole MR QD or 90 mg oral dexlansoprazole MR QD or 30 mg oral lansoprazole delayed release QD	639/629	380/300	49.0 (18-84)	4 or 8 weeks	Males and females ≥18 years of age with endoscopically confirmed EE.
							658/624	166/302	48.0 (18-85)		
							690/644	265/325	47.0 (18-87)		

EE=erosive esophagitis; F=female; M=male; MR=modified release; QD=once daily.

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>b</sup>						
						Study and Control Drugs Dose, Route, Regimen	Subjects by Arm Entered/ Completed	Gender M/F	Median Age (Range)	Duration of Treatment	Study Population and Primary Inclusion Criteria
I-EE04-085 United States, Australia, Bulgaria, Canada, Colombia, Czech Republic, Estonia, Germany, Hungary, India, Israel, Latvia, Lithuania, New Zealand, Peru, Poland, Russia, Slovakia, South Africa, and Ukraine	Complete Dec-05/Jan-07	156 2054/1950	Randomized, double-blind, active-controlled  Active	To assess the efficacy and safety in healing EE over 8 weeks of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to lansoprazole delayed-release capsules (30 mg QD) in healing EE over 8 weeks in subjects with endoscopically proven EE; the secondary objectives were to assess the efficacy of dexlansoprazole MR (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, fasting gastrin levels, and vital signs.						
						60 mg oral dexlansoprazole MR QD or 90 mg oral dexlansoprazole MR QD or 30 mg oral lansoprazole delayed release QD	694/641	377/317	48.5 (20-85)	4 or 8 weeks	Males and females ≥18 years of age with endoscopically confirmed EE.
							687/642	352/335	46.0 (19-90)		
							673/643	362/311	47.0 (18-85)		

EE=erosive esophagitis; F=female; M=male; MR=modified release; QD=once daily.

Source: Table 2.7.a., p. 22, Module 2.7.3, NDA 22-287

**(b) (4)** (dexlansoprazole)

A screening endoscopy was performed to determine the presence and assess the severity of EE. Severity of EE was graded based on the LA Classification System, a validated tool which focuses on the description of the extent of the visible mucosal breaks to define the severity of the disease. Grade A and Grade B are generally considered to be mild EE, while Grade C and Grade D represent moderate to severe EE.

Enrollment was targeted to include approximately 70% of subjects with LA Classification Grades A and B and approximately 30% of subjects with LA Grades C and D. Therefore, once subjects with LA Grades A and B comprised approximately 70% of total projected enrollment of 1950 subjects, primarily subjects with LA Grades C and D were enrolled. Ultimately, approximately 71% of enrolled subjects had LA Grade A or B, and 29% had Grade C or D (6% were Grade D).

**Medical Officer Comments:**

**The proportional enrollment of subjects with LA Grades A-D is representative of the actual patient population with erosive esophagitis and this strategy was agreed upon by the sponsor and the Division during presubmission meetings.**

Subjects who tested positive for *Helicobacter pylori* (*H. pylori*) were excluded from the study or were allowed into the study after an effective eradication therapy.

Subjects with Barrett's esophagus were excluded from all studies due to the potential risk for randomization of these subjects to the placebo arms in the long-term maintenance studies.

Clinical laboratory tests, including fasting serum gastrin, serum pregnancy tests (all females), and concomitant medication assessments were also performed. Subjects were instructed that lifestyle or behavior modifications designed to treat their symptoms of GERD should not be altered throughout the study. During screening, subjects completed QOL and symptom severity questionnaires, and investigators assessed subjects for heartburn, acid regurgitation, dysphagia, belching, and epigastric pain. In addition, screening evaluations included obtaining a complete medical and social history, complete physical examination including vital signs, and endoscopy (including gastric biopsies which were only taken if the subject had a maintenance of healed EE study available at their site that was still enrolling).

During the 8-week treatment period, subjects self-administered 1 capsule of blinded study drug once daily in the morning before breakfast and returned for study visits after 4 weeks and, if unhealed, 8 weeks of treatment. Subjects documented the presence and maximum severity of daytime and nighttime heartburn symptoms and recorded usage of rescue medication in a diary twice daily. At these visits, study drug was collected and/or dispensed, GERD symptoms were assessed, QOL and symptom severity questionnaires were completed, concomitant medication use was reviewed, and adverse events assessed.

An endoscopy was performed at Week 4. If the subject's EE was healed, the subject completed the study, and Final Visit procedures were performed. If the subject's EE was not healed, the subject continued in the study for an additional 4 weeks. For those subjects who continued in the

study, an endoscopy was also performed at Week 8.

If subjects successfully completed the study (i.e., EE was healed), they were eligible for enrollment in a 6-month maintenance study (Study T-EE05-135 or T-EE04-086) if a study was available at their site.

The 2 HEE studies enrolled a total of 4092 subjects at 188 sites in the US and 118 sites outside of the US. Of the 4059 intent-to-treat (ITT) subjects, 2929 participated at US sites and 1130 participated at sites outside of the US.

### 6.1.1.2 Eligibility Criteria

The following table displays the inclusion and exclusion criteria for both HEE studies.

**Table 7: Eligibility criteria for Studies T-EE04-084 and T-EE04-085**

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> <li>1. Prior to any study-specific procedures being performed, the subject voluntarily signed an Informed Consent Form (ICF) and any privacy statements/authorization form required by the region in which the subject participated, after having its contents fully explained and all questions answered. An Institutional Review Board approved the ICFs.</li> <li>2. Male or female subjects must have been <math>\geq 18</math> years of age (and of legal age of consent).</li> <li>3. All female subjects must have had a negative serum pregnancy test at screening and negative urine pregnancy test at Day -1 and were using, and agree to continued use of, a double-barrier method of birth control. Oral, injectable, or patch contraceptives may have been used as one method if the subject has been taking them for <math>&gt; 3</math> months duration at the Screening Visit. Subjects who have had a bilateral tubal ligation, hysterectomy, or were postmenopausal (the absence of menses for 1-2 years with an follicle-stimulating hormone level <math>\geq 40</math> IU/L or absence of menses for <math>&gt; 2</math> years) were not required to use birth control.</li> <li>4. Subject must have had endoscopically confirmed EE as defined by the Los Angeles (LA) Classification Grading System (A to D).</li> </ol>	<ol style="list-style-type: none"> <li>1. Subject tested positive for <i>H. pylori</i> based on the result of the Campylobacter-like organisms (CLO) test. In the US and Canada, a CLO test was performed only for subjects who tested positive for <i>H. pylori</i> by finger stick or serology at screening and had EE. For all other countries, a mandatory CLO test was used at screening to determine subject's <i>H. pylori</i> status.</li> <li>2. Use of prescription or nonprescription proton pump inhibitors (PPIs) during screening and throughout the study.</li> <li>3. Use of prescription or nonprescription histamine (<math>H_2</math>) receptor antagonists or sucralfate during screening and throughout the study.</li> <li>4. Chronic use (<math>&gt; 12</math> doses per month) of nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclo-oxygenase-2 NSAIDs within 30 days prior to the screening period and throughout the study; however, low-dose aspirin up to 325 mg per day was allowed.</li> <li>5. Use of antacids (except for study-supplied Gelusil [North and South American sites], or a similar equivalent approved antacid [sites outside of North and South America] during the Screening and Treatment Periods.</li> <li>6. Subjects using drugs with significant anticholinergic effects such as tricyclics who could not stay on a stable dose for 4 weeks prior to dosing and throughout the study.</li> <li>7. Subjects who could not discontinue the use of misoprostol or prokinetics prior to the first dose of study drug and throughout the study.</li> <li>8. Need for continuous anticoagulant therapy.</li> <li>9. Use of any investigational drug(s) within 30 days of screening.</li> <li>10. Cancer (except basal cell carcinoma of the skin) within 5 years prior to screening.</li> <li>11. Any condition that may have required inpatient surgery during the course of the study.</li> <li>12. Endoscopic Barrett's esophagus and/or definite dysplastic changes in the esophagus. If any suspicious Barrett's esophagus was seen during screening and the principal investigator was confident that the subject Endoscopic Barrett's esophagus and/or definite dysplastic changes in the esophagus. If any suspicious Barrett's esophagus was seen during screening and the principal investigator was confident that the subject would be confirmed with Barrett's, the subject may have been automatically excluded. Otherwise, any suspicious Barrett's esophagus seen during screening endoscopy was biopsied and sent to a local pathology laboratory. Subjects may have been randomized; however, the subject must have been discontinued if the screening biopsy was found to confirm Barrett's and/or to have definite dysplastic changes. If the subject was discontinued, Final Visit procedures must have been performed, with the exception of the endoscopy. Subjects with indeterminate dysplasia due to severe inflammation may have been enrolled and rebiopsied at the next endoscopy.</li> <li>13. Subjects with a history of dilation of esophageal strictures, other than a Schatzki's ring (a ring of mucosal tissue near the lower esophageal sphincter).</li> <li>14. Subjects with active gastric or duodenal ulcers within 4 weeks of the first dose of study drug.</li> <li>15. Coexisting diseases that affected the esophagus (eg, esophageal varices, scleroderma, viral, fungal infection, or esophageal stricture), history of radiation therapy or cryotherapy to the esophagus, caustic or physiochemical trauma such as sclerotherapy to the esophagus.</li> <li>16. Evidence of uncontrolled systemic disease.</li> <li>17. Subject had abnormal laboratory values that suggested a clinically significant underlying disease or condition that may have prevented the subject from entering the study; or subject with the following lab abnormalities: creatinine <math>&gt; 1.5</math> mg/dL, ALT and/or AST <math>&gt; 2.5 \times</math> the upper limits of normal, or bilirubin <math>&gt; 2.0</math> mg/dL with AST/ALT elevated above normal values.</li> <li>18. Subject known to have acquired immunodeficiency syndrome. Current or historical evidence of Zollinger-Ellison syndrome or other hypersecretory condition.</li> </ol>

Inclusion Criteria	Exclusion Criteria
	19. History of gastric, duodenal, or esophageal surgery except simple oversew of an ulcer. 20. Acute upper gastrointestinal hemorrhage within 4 weeks of the screening endoscopy. 21. Subject had received blood products within 3 months prior to the first dose of study drug. 22. Known hypersensitivity to any PPI (including lansoprazole, omeprazole, rabeprazole, pantoprazole, or esomeprazole), any component of dexlansoprazole MR, or Gelusil/antacid. 23. Females who were pregnant or lactating. 24. History of alcohol abuse ( $\geq 21$ units [1 unit=12 oz beer, 1.5 oz hard liquor, or 5 oz wine] per week) or illegal drug use or drug addiction in the 12 months prior to screening. 25. Subjects who, in the opinion of the investigator, were unable to comply with the requirements of the study or were unsuitable for any reason.

Source: Table 2.7.f, p.33-34, Module 2.7.3, NDA 22-287

### 6.1.1.3 Efficacy Endpoints

An overview of the endpoints for the two studies is presented below:

#### Primary Efficacy Variable

- The percentage of subjects who had complete healing of EE over 8 weeks as assessed by endoscopy.

The primary analyses were based on the crude healing rates determined as the proportion of subjects whose EE was healed, as assessed by endoscopy (LA Grade=0). ITT subjects who had  $\geq 1$  postbaseline endoscopic assessment were included in the analysis. Additionally, endoscopies that were conducted  $>7$  days after the last dose of study drug were not included in the analysis. The crude healing rates were calculated by dividing the number of healed subjects by the number of subjects with  $\geq 1$  postbaseline endoscopy assessment. Subjects who were healed by Week 4 were carried forward as healed to the Week 8 healing rates. Subjects who were not healed by Week 4 endoscopy assessment and did not have Week 8 endoscopic assessment were considered not healed by Week 8.

#### Secondary Efficacy Variable

- The percentage of subjects who had complete healing of EE over 4 weeks as assessed by endoscopy.
- The percentage of subjects with baseline LA Grade C or D (moderate or severe) who had complete healing of EE over 8 weeks as assessed by endoscopy.

#### Additional Efficacy Variables

- The percentage of subjects with baseline LA Grade C or D who had complete healing of EE by Week 4, as assessed by endoscopy.
- The percentage of subjects who had complete healing of EE over 8 weeks as assessed by endoscopy by Baseline LA Grade (A, B, C, D).

**(b) (4)** dexlansoprazole)

- The percentage of days with neither daytime nor nighttime heartburn (24-hour heartburn free days) and days without nighttime heartburn during treatment, as assessed by subject's daily diary.
- The mean severity of daytime and nighttime heartburn and mean severity of nighttime heartburn during treatment, as assessed by daily diary.
- The time to sustained resolution of diary-recorded heartburn defined as 7 consecutive 24-hour heartburn-free days, as assessed by daily diary in each study.
- The percentage of days without rescue medication during treatment as assessed by daily diary.
- The change from baseline in PAGI-SYM and PAGI-QOL measurements to Final Visit.
- Investigator assessed GERD symptom severity summarized for Final Visit.

**Medical Officer Comments:**

The sponsor chose a large number of secondary endpoints for study; however, they have designated two of these as "secondary," while the others are considered "additional." Since a hierarchical testing strategy was employed for the "secondary" endpoints and they could potentially be included in labeling, the reviewer has renamed these as "key secondary endpoints." However, the sponsor-designated "additional endpoints" will not be eligible for inclusion in labeling. Moreover, the reviewer believes that these endpoints provide a relatively insignificant contribution toward demonstrating the efficacy of the product when compared to the primary and key secondary efficacy findings. For these reasons, the reviewer has chosen not to present a written review of these endpoints and will instead focus on presenting a detailed review of the primary and "key secondary" efficacy data.

6.1.1.4 Statistical Considerations

The sponsor chose to perform a noninferiority study with sequential superiority testing if noninferiority was demonstrated.

Noninferiority was determined by calculating 95% confidence intervals (CI) for the differences between the healing rates of each dex dose and that of lansoprazole 30 mg (primary efficacy endpoint). If the lower bound of that CI was greater than -10%, noninferiority was concluded. Superiority for the primary endpoint was then assessed by comparing healing rates. When comparing 2 doses of dexlansoprazole MR to lansoprazole 30 mg, the overall significance level of 0.05 was controlled using Hochberg's method.

Superiority testing was then carried out for the 2 key secondary endpoints, and multiplicities were again controlled to maintain an overall significance level at 0.05.

**Medical Officer Comments:**

The sponsor appears to have designed these studies to maintain acceptable Type I error control for the multiple comparisons between different dex doses for the primary and key secondary endpoints. However, final determination of the statistical soundness of the sponsor's methods will be made by the Biostatistics reviewers for this application. Please see their respective reviews for a more detailed analysis.

#### 6.1.1.5 Noninferiority Margin: Clinical Considerations

To assure that the sponsor’s chosen noninferiority margin of -10% was clinically meaningful, the reviewer performed an analysis of the historical performance of lansoprazole 30 mg daily when compared to placebo for HEE.

The following table illustrates the large treatment difference of lansoprazole 30 mg daily when compared to placebo for HEE (48.5% at Week 4, 42.9% at Week 8). In addition, although the sample sizes are relatively small for this study, a strong statistical difference is seen ( $p \leq 0.001$ ).

**Table 8: Efficacy of Lansoprazole vs. Placebo in NDA 20-406**

Week	PREVACID			Placebo (N=63)
	15 mg q.d. (N=69)	30 mg q.d. (N=65)	60 mg q.d. (N=72)	
4	67.6%	81.3%**	80.6%**	32.8%
6	87.7%*	95.4%*	94.3%*	52.5%
8	90.9%*	95.4%*	94.4%*	52.5%

\*( $p \leq 0.001$ ) versus placebo.

\*\*( $p \leq 0.05$ ) versus PREVACID 15 mg and placebo.

Source: NDA 20-406 Clinical Review\*\*

#### Medical Officer Comments:

Based on the sponsor’s proposed margin of -10%, dex would be considered noninferior to lansoprazole 30 mg daily if it showed a healing rate for which the lower bound of the 95% CI was 85.4% or greater. This would translate to at least a 32.9% treatment difference when compared to placebo. The reviewer believes that this margin is clinically meaningful, and thus agrees with the sponsor’s choice of margin of -10% when demonstrating noninferiority versus the active comparator lansoprazole 30 mg daily.

#### 6.1.2 Demographics/Baseline Characteristics

The following table presents the integrated demographics and baseline characteristics of the intention-to-treat (ITT) population from both HEE studies.



The following table presents variables that pertain to the social history of enrolled subjects.

**Table 10: Social History: Integrated Analysis of Studies T-EE04-084 and T-EE04-085**

Variable	Dexlansoprazole MR		Lansoprazole 30 mg QD (N=1356) n (%)	All ITT Subjects (N=4059) n (%)
	60 mg QD (N=1358) n (%)	90 mg QD (N=1345) n (%)		
Alcohol Use				
Drinker	776 (57.1)	765 (56.9)	748 (55.3)	2289 (56.4)
Non-/Ex-drinker	582 (42.9)	580 (43.1)	605 (44.7)	1767 (43.6)
Smoking Status				
Smoker	316 (23.3)	318 (23.6)	340 (25.1)	974 (24.0)
Non-/Ex-smoker	1042 (76.7)	1027 (76.4)	1015 (74.9)	3084 (76.0)
Caffeine Use				
Caffeine User	1044 (76.9)	1068 (79.4)	1079 (79.7)	3191 (78.7)
Non-caffeine User	314 (23.1)	277 (20.6)	275 (20.3)	866 (21.3)

Source: Table 2.7.h, p. 37, Module 2.7.3, NDA 22-287

More than half of the ITT subjects used alcohol; the majority of subjects were non-/ex-smokers and the majority used caffeine. No statistically significant differences were observed among treatment groups for any of these characteristics.

**Medical Officer Comments:**

Use of any of these substances is known to worsen gastroesophageal reflux and could potentially have confounded the study results. However, it appears that use of these substances was well-balanced among the study drug and active control treatment arms.

The following table shows the baseline LA Grade and *H. pylori* status of enrolled subjects.

**Table 11: Baseline LA Grade & Baseline *H. pylori* Status:  
 Integrated Analysis of Studies T-EE04-084 and T-EE04-085**

LA Grade	Dexlansoprazole MR		Lansoprazole 30 mg QD (N=1356) n (%)	All ITT Subjects (N=4059) n (%)
	60 mg QD (N=1358) n (%)	90 mg QD (N=1345) n (%)		
A	467 (34.4)	511 (38.0)	452 (33.3)	1430 (35.2)
B	501 (36.9)	452 (33.6)	502 (37.0)	1455 (35.8)
C	313 (23.0)	299 (22.2)	319 (23.5)	931 (22.9)
D	77 (5.7)	83 (6.2)	83 (6.1)	243 (6.0)

<i>H. pylori</i> Status <sup>a</sup>	Dexlansoprazole MR		Lansoprazole 30 mg QD (N=1356) n (%)	All ITT Subjects (N=4059) n (%)
	60 mg QD (N=1358) n (%)	90 mg QD (N=1345) n (%)		
Positive	16 (1.2)	25 (1.9)	21 (1.5)	62 (1.5)
Negative	1337 (98.5)	1315 (97.8)	1330 (98.1)	3982 (98.1)
Unknown	5 (0.4)	5 (0.4)	5 (0.4)	15 (0.4)

Source: Tables 2.7.i & 2.7.j, p. 38, Module 2.7.3, NDA 22-287

(b) (4) (dexlansoprazole)

Approximately 71% of subjects had LA Grade A or B, and 29% had LA Grade C or D. The percentages of subjects in each classification grade were similar among all treatment groups. In addition, the majority of subjects had negative *H. pylori* test results at baseline (98.1%). No statistically significant differences were observed among treatment groups for either variable.

The following table shows baseline subject diary variables and helps to characterize the frequency and severity of enrollees' heartburn, the most common symptom reported by patients with GERD and EE.

**Table 12: Baseline Number of Days and Mean Severity of Heartburn:  
 Integrated Analysis of Studies T-EE04-084 & T-EE04-085**

Variable	Dexlansoprazole MR		Lansoprazole	All ITT
	60 mg QD (N=1358) n (%)	90 mg QD (N=1345) n (%)	30 mg QD (N=1356) n (%)	Subjects (N=4059) n (%)
<b>Number of Days With Daytime/Nighttime Heartburn</b>				
0-3	201 (15)	221 (16)	207 (15)	629 (15)
4-5	266 (20)	230 (17)	238 (18)	734 (18)
6-7	851 (63)	854 (63)	866 (64)	2571 (63)
N	1318	1305	1311	3934
Mean (SD)	5.6 (1.9)	5.5 (1.9)	5.6 (1.9)	5.6 (1.9)
Median	6.0	6.0	6.0	6.0
<b>Number of Days With Nighttime Heartburn</b>				
0-3	510 (38)	515 (38)	491 (36)	1516 (37)
4-5	264 (19)	258 (19)	284 (21)	806 (20)
6-7	541 (40)	529 (39)	531 (39)	1601 (39)
N	1315	1302	1306	3923
Mean (SD)	4.2 (2.4)	4.2 (2.5)	4.2 (2.4)	4.2 (2.5)
Median	5.0	5.0	5.0	5.0
Variable	Dexlansoprazole MR		Lansoprazole	All ITT
	60 mg QD (N=1358) n (%)	90 mg QD (N=1345) n (%)	30 mg QD (N=1356) n (%)	Subjects (N=4059) n (%)
<b>Mean Severity of Daytime/Nighttime Heartburn<sup>a</sup></b>				
0 to <1	458 (34)	473 (35)	459 (34)	1390 (34)
1 to <2	550 (41)	520 (39)	552 (41)	1622 (40)
2 to <3	246 (18)	249 (19)	251 (19)	746 (18)
3 to 4	64 (5)	63 (5)	49 (4)	176 (4)
N	1318	1305	1311	3934
Mean (SD)	1.38 (0.82)	1.37 (0.84)	1.36 (0.81)	1.37 (0.82)
Median	1.29	1.29	1.29	1.29
<b>Mean Severity of Nighttime Heartburn<sup>a</sup></b>				
0 to <1	482 (35)	519 (39)	516 (38)	1517 (37)
1 to <2	469 (35)	443 (33)	445 (33)	1357 (33)
2 to <3	283 (21)	262 (19)	277 (20)	822 (20)
3 to <4	81 (6)	78 (6)	68 (5)	227 (6)
N	1315	1302	1306	3923
Mean (SD)	1.32 (0.94)	1.29 (0.94)	1.28 (0.91)	1.30 (0.93)
Median	1.29	1.17	1.15	1.17

Source: Tables 2.7.k, 2.7.l, p. 39-40, Module 2.7.3, NDA 22-287

63% of subjects had 6 to 7 days of daytime or nighttime (daytime/nighttime) heartburn at baseline and 39% had 6 to 7 days with nighttime heartburn at baseline. There were no statistically significant differences among treatment groups for these variables.

The overall median of the mean severity of daytime/nighttime heartburn and of nighttime heartburn was mild to moderate (1.29). No statistically significant differences were observed among treatment groups for these variables.

**Medical Officer Comments:**

Once again, the treatment groups were well-balanced for all variables analyzed.

Based on the demographic/baseline tables presented above, randomization appears to have been adequate in minimizing the effect of those covariates which could reasonably be expected to confound the analysis of the study results.

6.1.3 Drug Exposure/Compliance/Patient Disposition

6.1.3.1 Drug Exposure

The following table presents the study drug exposure for both HEE studies.

**Table 13: Study Drug Exposure for ITT Subjects:  
 Integrated Analysis of Studies T-EE04-084 and T-EE04-085**

Total Days on Study Drug	Dexlansoprazole MR		Lansoprazole	All Subjects
	60 mg QD (N=1358) n (%)	90 mg QD (N=1345) n (%)	30 mg QD (N=1356) n (%)	(N=4059) n (%)
1-<14	29 (2)	21 (2)	17 (1)	67 (2)
14-<28	196 (14)	173 (13)	165 (12)	534 (13)
28-<56	794 (58)	833 (62)	786 (58)	2413 (59)
≥56	339 (25)	318 (24)	388 (29)	1045 (26)
Mean±SD	38.5±15.01	38.2±14.79	39.8±15.25	38.8±15.03
Minimum-Maximum	1-82	1-82	1-97	1-97
<b>Cumulative Days on Study Drug</b>				
≥1	1358 (100)	1345 (100)	1356 (100)	4059 (100)
≥14	1329 (98)	1324 (98)	1339 (99)	3992 (98)
≥28	1133 (83)	1151 (86)	1174 (87)	3458 (85)
≥56	339 (25)	318 (24)	388 (29)	1045 (26)

Source: Table 2.7.d., p.31, Module 2.7.3, NDA 22-287

The majority (85%) of subjects completed ≥28 days of treatment.

**(b) (4)** (dexlansoprazole)

**Medical Officer Comments:**

**Study drug exposure appears to have been similar among the three treatment arms.**

6.1.3.2 Study Drug Compliance

The following table shows the study drug and diary compliance for subjects in the two HEE studies.

**Table 14: Study Drug Compliance for ITT Subjects:  
 Integrated Analysis of Studies T-EE04-084 and T-EE04-085**

Study Drug Compliance	Dexlansoprazole MR		Lansoprazole 30 mg QD (N=1356)	All ITT Subjects (N=4059)
	60 mg QD (N=1358)	90 mg QD (N=1345)		
<90%: n (%)	101 (7)	90 (7)	92 (7)	283 (7)
≥90%: n (%)	1257 (93)	1255 (93)	1264 (93)	3776 (93)
Mean (SD)	97.4 (5.93)	97.5 (6.13)	97.5 (6.06)	97.5 (6.04)
Median	100.0	100.0	100.0	100.0
Minimum-Maximum	20-100	0-100	17-100	0-100

Diary Compliance	Dexlansoprazole MR		Lansoprazole 30 mg QD (N=1356)	All ITT Subjects (N=4059)
	60 mg QD (N=1358)	90 mg QD (N=1345)		
<b>Percentage of Expected Entries</b>				
<50%: n (%)	62 (5)	55 (4)	75 (6)	192 (5)
50-80%: n (%)	93 (7)	90 (7)	106 (8)	289 (7)
80-90%: n (%)	80 (6)	89 (7)	80 (6)	249 (6)
≥90%: n (%)	1095 (81)	1072 (80)	1068 (79)	3235 (80)
Missing <sup>†</sup>	28 (2)	39 (3)	27 (2)	94 (2)
N	1330	1306	1329	3965
Mean (SD)	90.8 (16.25)	91.1 (15.27)	90.1 (17.55)	90.7 (16.39)
Median	96.4	96.4	96.4	96.4
Minimum-Maximum	1-100	1-100	1-100	1-100

Source: Tables 2.7.m. & 2.7.n., p. 41-42, Module 2.7.3, NDA 22-287

The majority of subjects (93%) were ≥ 90% compliant with study drug use during the studies. Likewise, the majority of subjects (80%) completed ≥ 90% of expected diary entries.

**Medical Officer Comments:**

**The above rates of study drug compliance should have afforded an adequate evaluation of the drug's efficacy.**

### 6.1.3.3 Patient Disposition

The following table illustrates the reasons for premature discontinuation from the HEE studies.

**Table 15: Summary of Primary Reasons for Premature Discontinuation:  
 Integrated Analysis of Studies T-EE04-084 and T-EE04-085**

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

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

Source: Table 2.7.o., p. 43, Module 2.7.3, NDA 22-287

The overall number of subjects who prematurely discontinued was low ( $\leq 8\%$ ). However, a statistically significant difference between the dexlansoprazole MR 60-mg QD and lansoprazole 30-mg QD treatment groups was observed for the percentage of subjects who prematurely discontinued for any reason (8% vs. 6%, respectively) and for percentage of subjects who prematurely discontinued due to adverse events (2% vs. 1%, respectively). The incidence of each was greater in the dexlansoprazole MR 60-mg QD treatment group compared with the lansoprazole 30-mg QD treatment group.

**Medical Officer Comments:**

While statistically significant, the rates of premature discontinuations for any reason and for adverse events were higher in one of the study drug arms (60 mg dose) rather than in the active comparator. Since these discontinued subjects would have been considered treatment failures, treatment difference would have been slightly more difficult to demonstrate (i.e., higher dropouts in study drug arm favors active comparator). For this reason, the reviewer does not believe this imbalance compromises the analysis of the product's efficacy for this indication.

#### 6.1.4 Analysis of Primary Endpoint

As discussed in Section 6.1.1.3 above, the primary endpoint for both HEE studies was the percentage of subjects who had complete healing of EE by Week 8.

As prespecified in the protocol and original statistical analysis plan (SAP), the primary analysis for the primary and secondary efficacy endpoints was based on the life-table method, and for those endpoints, crude rate analysis was considered supportive. Based on a recommendation from the Food and Drug Administration at the pre-New Drug Application (pre-NDA) meeting on 1 October 2007, the primary analysis for the primary and secondary endpoints was changed to crude rate analysis, and analysis based on life-table methods was considered supportive.

The primary analyses were based on the crude healing rates determined as the proportion of subjects whose EE was healed, as assessed by endoscopy (LA Grade=0). ITT subjects who had  $\geq 1$  postbaseline endoscopic assessment were included in the analysis. Additionally, endoscopies that were conducted  $>7$  days after the last dose of study drug were not included in the analysis. The crude healing rates were calculated by dividing the number of healed subjects by the number of subjects with  $\geq 1$  postbaseline endoscopy assessment. Subjects who were healed by Week 4 were carried forward as healed to the Week 8 healing rates. Subjects who were not healed by Week 4 endoscopy assessment and did not have Week 8 endoscopic assessment were considered not healed by Week 8.

Supportive analysis of the primary efficacy endpoint for ITT subjects was based on life-table methods. The life-table method calculated EE healing rates considering 2 intervals. Treatment group comparisons of the healing rates were done using log-rank tests with day as a discrete time unit, which was independent of the intervals that were used for the healing rate estimations. Endoscopies that were performed  $>7$  days after the last day of study drug were not included in the analyses. The healing rate by Week 8 was the percentage of subjects who were healed by Day 70 and within 7 days of postdosing according to endoscopic assessment. The last endoscopic assessment for each subject was included in the analysis of Week 8 healing rates. A subject who was not healed was censored on the day the endoscopy was performed. A subject without a postbaseline endoscopy within 7 days after the last day of study drug was included but was considered censored data.

The differences in the healing rates between treatments were calculated by subtracting the estimated healing rate by life table for lansoprazole from the estimated healing rates by life table for each dexlansoprazole MR dose.

**Medical Officer Comments:**

**This endpoint was accepted by the agency during meetings with the sponsor prior to the current NDA submission, and is consistent with primary endpoints for this indication for other PPIs. The methods described above for the primary and supportive analysis for this primary endpoint appear acceptable.**

(b) (4) (dexlansoprazole)

The following table shows both the primary (crude rate) and supportive (life table) analyses for the primary endpoint for each individual study and for the integrated analysis of both studies.

**Table 16: Week 8 Healing Rates of Erosive Esophagitis: ITT Subjects**

Data Set Analysis	Dexlansoprazole MR		Lansoprazole 30 mg QD % (95% CI)	p-value		
	60 mg QD % (95% CI)	90 mg QD % (95% CI)		Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	Dex MR 60 mg vs Dex MR 90 mg
<b>Study T-EE04-084</b>						
By Crude (Primary) <sup>a</sup>	(N=639) 85.3 (82.3, 87.9)	(b) (4) (b) (4)	(N=656) 79.0 (75.6, 82.0)	0.004*	(b) (4)	(b) (4)
By Life Table (Supportive) <sup>b</sup>	(N=673) 92.3 (90.0, 94.7)	(b) (4) (b) (4)	(N=684) 86.1 (83.0, 89.2)	0.060	(b) (4)	(b) (4)
<b>Study T-EE04-085</b>						
By Crude (Primary) <sup>a</sup>	(N=657) 86.9 (84.1, 89.4)	(b) (4) (b) (4)	(N=648) 84.6 (81.6, 87.3)	0.234	(b) (4)	(b) (4)
By Life Table (Supportive) <sup>b</sup>	(N=685) 93.1 (90.9, 95.3)	(b) (4) (b) (4)	(N=672) 91.5 (89.0, 93.9)	0.167	(b) (4)	(b) (4)
<b>Integrated Analysis</b>						
By Crude (Primary) <sup>a</sup>	(N=1296) 86.1 (84.1, 87.9)	(b) (4) (b) (4)	(N=1304) 81.7 (79.5, 83.8)	0.003*	(b) (4)	(b) (4)
By Life Table (Supportive) <sup>b</sup>	(N=1358) 92.7 (91.1, 94.4)	(b) (4) (b) (4)	(N=1356) 88.9 (87.0, 90.9)	0.021*	(b) (4)	(b) (4)

Note: Endoscopic assessments conducted  $\geq 7$  days after the last dose of study drug are excluded.

CI=confidence interval; Dex MR=dexlansoprazole MR; Lanso=lansoprazole 30 mg QD.

a Primary analysis: p-values are from CMH test with Baseline LA Grade as strata.

b Supportive analysis: p-values are from log-rank test with day as a discrete time unit.

\* Dexlansoprazole MR treatment group is statistically significantly superior to lansoprazole 30 mg QD using Hochberg's method at the nominal level of 0.05.

Source: Table 2.7.p., p. 45, Module 2.7.3, NDA 22-287

Looking first at the primary analysis (crude rates), both dex MR 60 mg QD and 90 mg QD were noninferior to lansoprazole 30 mg QD for overall healing of EE at Week 8 in each study as well as in the integrated analysis.

In addition, dex MR 90 mg QD and 60 mg QD demonstrated statistically significant superiority over lansoprazole 30 mg QD in Study T-EE04-084 (therapeutic gains of 7 and (b) (4) percentage points, respectively).

In Study T-EE04-085, dex MR 90 mg QD also demonstrated statistically significant superiority over lansoprazole 30 mg QD, with a therapeutic gain of approximately (b) (4) percentage points. However, dex 60 mg QD failed to show a statistically significant superiority over lansoprazole for this study.

In the integrated analysis, both dex MR 90 mg QD and 60 mg QD were statistically significantly superior over Lansoprazole 30 mg QD (therapeutic gains of (b) (4) and 4 percentage points, respectively).

(b) (d) (dexlansoprazole)

In addition, there was no significant difference seen between dex 90 mg and dex 60 mg in either study or in the integrated analysis.

**Medical Officer Comments:**

As would be expected for the PPIs when used for this indication, the healing rates seen above are quite high both for the study drug and for the active comparator (min 79%). When examining the point estimates, dex 90 mg is clearly statistically superior to lansoprazole in both studies as well as in the integrated analysis.

What is more difficult to determine, however, is the clinical relevance of this superiority. Looking first at Study T-EE04-085, the treatment difference is modest<sup>(b) (4)</sup>, and there is overlap between the 95% CIs of the healing rates for the two drugs (lower bound for dex 90 mg<sup>(b) (4)</sup> vs. upper bound for lansoprazole=87.3). Given this, it is equally probable that the actual healing rate comparison would favor lansoprazole by 0.5%.

The treatment difference shown in Study T-EE04-084 is larger<sup>(b) (4)</sup> and more significant<sup>(b) (4)</sup> than that seen in Study T-EE04-085, but even in Study -084 the 95% CIs nearly overlap (lower bound for dex 90 mg<sup>(b) (4)</sup> vs. upper bound for lansoprazole=82.0).

The integrated analysis shows even greater statistical significance for the treatment difference than either individual study ( $p < 0.001$ ) and there is no overlap between the 95% CIs, but a pooled analysis should not form the basis for demonstrating clinical relevance of a treatment difference.

Taking all of these factors into account, the reviewer believes that the treatment differences between dex 90 mg and lansoprazole in each study, while statistically significant, are not clinically meaningful<sup>(b) (4)</sup>

(b) (4)

b) (4)

Treatment differences from the supportive life-table analyses were generally consistent with those from the crude rate analyses. In Study T-EE04-084, both dex MR 60 mg QD and dex MR 90 mg QD approached statistically significant superiority compared to lansoprazole 30 mg QD.

In Study T-EE04-085, dex MR 90 mg QD approached statistically significant superiority over lansoprazole 30 mg QD. However, dex MR 60 mg QD failed to show statistically significant superiority over lansoprazole 30 mg QD for this study.

Both dex MR 60 mg QD and dex MR 90 mg QD were statistically significantly superior to lansoprazole 30 mg QD in the integrated analysis.

There was no significant difference seen between dex 90 mg and dex 60 mg in either study or in the integrated analysis.

(b) (4) (dexlansoprazole)

**Medical Officer Comments:**

The reviewer agrees that the results from the life-table analyses are generally consistent with the crude rate analysis. As with the crude rate analysis, numerical differences between dex and lansoprazole are small (6.2% maximum) with overlapping CIs demonstrated for healing rates of the drugs in Study T-EE04-085. Statistically significant superiority (for both doses vs. lansoprazole) was seen only in the integrated analysis and not in either individual study.

6.1.5 Analysis of Secondary Endpoints

As both dexlansoprazole MR treatment groups were noninferior to lansoprazole in the analysis from each study and the integrated analysis, the secondary efficacy endpoints were assessed for superiority to lansoprazole 30 mg QD. The 2 secondary efficacy variables were: (1) the percentage of subjects with baseline LA Grades of moderate or severe (C or D) combined who had complete healing of EE over 8 weeks, as assessed by endoscopy and (2) the percentage of subjects who had complete healing of EE over 4 weeks as assessed by endoscopy.

6.1.5.1 Week 8 Healing Rates by Baseline LA Grade C or D

The following table portrays the results for the first key secondary endpoint.

**Table 17: Week 8 Healing Rates by Baseline LA Grade C or D**

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

Source: Table 2.7.q., p.48, Mod (b) (4) DA 22-287

**(b) (4)** (dexlansoprazole)

In Study T-EE04-084, from the primary analysis of Week 8 crude healing rates for subjects with baseline LA Grade C or D, the dex MR 60 mg QD group was statistically significantly superior to the lansoprazole 30 mg QD group, with a therapeutic gain of 15 percentage points. Dex MR 90 mg QD showed a therapeutic gain of <sup>(b)</sup> percentage points; however, it was not statistically significantly superior to lansoprazole 30 mg QD <sup>(b) (4)</sup> due to the Hommel-Simes' multiplicity adjustment for the <sup>(b)</sup> <sub>(4)</sub> secondary efficacy endpoints. No statistically significant differences were observed between the 2 dex MR doses by either analysis.

In Study T-EE04-085, from the primary analysis of Week 8 crude healing rates for subjects with baseline EE grades of moderate or severe (LA Grades C or D), the dex MR 90 mg QD treatment group showed a therapeutic gain of <sup>(b)</sup> percentage points over lansoprazole 30 mg QD, and dex MR 60 mg QD showed a similar healing <sup>(4)</sup> rate as lansoprazole 30 mg QD. Neither dex MR dose, however, was statistically significantly superior to lansoprazole 30 mg QD. In an additional comparison, the dex MR 90 mg QD treatment group was statistically significantly superior to dexlansoprazole MR 60 mg QD <sup>(b) (4)</sup> without a multiplicity adjustment) for healing subjects with baseline EE grades of moderate or severe (LA Grade C or D); the difference between the crude healing rates was <sup>(b)</sup> <sub>(4)</sub> percentage points at Week 8.

In the integrated analysis of both studies, dexlansoprazole MR 90 mg QD demonstrated statistically significantly superior healing rates as compared to lansoprazole 30 mg QD by both the crude rate and life-table methods. Dexlansoprazole MR 60 mg QD was not statistically significantly superior to lansoprazole 30 mg QD by either method. There were no statistically significant differences observed between the two dexlansoprazole MR doses by either analysis.

**Medical Officer Comments:**

The reviewer is primarily interested in the crude rates since this was the preferred method of analysis recommended at the pre-NDA meeting. The first study showed a statistically significant therapeutic gain for the 60 mg dose when compared to lansoprazole 30 mg (15 percentage points higher), but this dose failed to show a similarly significant gain in the second study (-085) or in the integrated analysis. In fact, the treatment response for the lansoprazole group was slightly higher than that of the dex 60 mg group for the second study.

The 90 mg dex dose did not show statistical superiority in either study when compared to the active comparator. Although the sponsor compared the 90 mg treatment group to the 60 mg group and found a statistically significant difference, no adjustments for multiplicity were made <sup>(b) (4)</sup>.

The integrated analysis showed statistical superiority for the 90 mg dose when compared to lansoprazole, but the reviewer does not believe that a pooled analysis should be the basis for a claim of superiority over currently available therapy. The sponsor's rationale for performing the integrated analysis is that the individual studies were underpowered to detect a significant difference for this endpoint. The reviewer does not agree with this argument, however, since the purpose of performing integrated analyses of efficacy is to confirm the findings of the individual trials, not to provide adequate power to detect a

(b) (4) dexlansoprazole)

treatment difference. In fact, the Division’s objections to this methodology were conveyed to the sponsor during the pre-NDA meeting held in October 2007, as follows: “The combining or pooling of studies to show a clinically and statistically significant effect within a subgroup would generally be considered an exploratory analysis. The statistical significance and clinical benefit of dexlansoprazole MR 90 mg over lansoprazole 30 mg should be demonstrated within the individual studies as prospectively planned.”

With all of these factors in mind, the reviewer does not believe that either dose of dexlansoprazole demonstrated sufficient statistical superiority over Lansoprazole 30 mg for the key secondary endpoint of “Healing rates at Week 8 for Baseline LA Grade C & D,” (b) (4) for this indication.

6.1.5.2 Week 4 Overall Healing Rates

The following table shows the results for the second key secondary endpoint.

**Table 18: Week 4 Overall Healing Rates**

Data Set Analysis	Dexlansoprazole MR		Lansoprazole 30 mg QD % (95% CI)	p-value		
	60 mg QD % (95% CI)	90 mg QD % (95% CI)		Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	Dex MR 60 mg vs Dex MR 90 mg
<b>Study T-EE04-084</b>						
Week 4 by Crude (Primary) <sup>a</sup>	(N=639) 66.2 (62.4, 69.9)	(b) (4)	(N=656) 64.8 (61.0, 68.4)	0.705	(b) (4)	
Week 4 by Life Table (Supportive) <sup>b</sup>	(N=673) 77.0 (73.5, 80.5)	(b) (4)	(N=684) 76.5 (73.0, 80.0)	0.896	(b) (4)	
<b>Study T-EE04-085</b>						
Week 4 by Crude (Primary) <sup>a</sup>	(N=657) 69.7 (66.0, 73.2)	(b) (4)	(N=648) 65.4 (61.6, 69.1)	0.100	(b) (4)	
Week 4 by Life Table (Supportive) <sup>b</sup>	(N=685) 80.1 (76.8, 83.3)	(b) (4)	(N=672) 77.0 (73.4, 80.5)	0.117	(b) (4)	
<b>Integrated Analysis</b>						
Week 4 by Crude (Primary) <sup>a</sup>	(N=1296) 68.0 (65.4, 70.5)	(b) (4)	(N=1304) 65.1 (62.5, 67.7)	0.154	(b) (4)	
Week 4 by Life Table (Supportive) <sup>b</sup>	(N=1358) 78.6 (76.2, 81.0)	(b) (4)	(N=1356) 76.7 (74.2, 79.2)	0.287	(b) (4)	

Source: Table 2.7.r., p.50, Module 2.7.3, NDA 22-287

No statistically significant differences were seen between the two dex groups and lansoprazole for this secondary endpoint in either study.

**Medical Officer Comments:**

It is interesting that the treatment differences seen at this juncture (Week 4) for both doses of dex are even smaller than those seen for the primary endpoint (Week 8). This would seem to indicate a trend toward superior efficacy for dex over Lansoprazole when used for longer periods of time; (b) (4)

Clinical Review  
Keith B. St. Amand, MD  
NDA 22-287  
**(b) (4)** (dexlansoprazole)

### 6.1.6 Subpopulations

The sponsor performed comparisons of the dex 60 mg and 90 mg groups with Lansoprazole 30 mg for the primary endpoint for the following subgroups:

- Age
- Race
- Gender
- BMI
- Smoking Status
- Alcohol Use
- Caffeine Use
- Baseline LA Grade
- Combined Baseline LA Grade (Grade A& B vs. Grade C& D)
- Baseline Diary Recorded Heartburn
- Overall Study Drug Compliance
- Baseline GERD Symptom Investigator Assessment of Heartburn
- US vs. ex-US Investigative Site
- US vs. ex-US Investigative Site by Combined Baseline LA Grade
- Rescue Medication Usage

In Study T-EE04-084, results of the primary analysis adjusted for the various subgroup factors were similar to those from the primary efficacy analysis with respect to statistically significant superiority for dex MR 60 mg QD and 90 mg QD compared to lansoprazole 30 mg QD.

In Study T-EE04-085, all of these subgroup analyses, except for the alcohol use and investigative site as factors, showed results consistent with the primary crude rate analysis: the dex MR 90 mg QD treatment group was statistically significantly superior to the lansoprazole 30 mg QD treatment group, while the dex 60 mg treatment group was not.

In the integrated analysis, the results from the subgroup efficacy analyses were similar to those from the primary efficacy analysis, with statistically significant superiority for dex MR 60 mg QD and 90 mg QD compared to lansoprazole 30 mg QD after adjusting for each of these factors.

Major relevant demographic factors (age, race, gender, and BMI) were included in the subgroup analyses to assess whether the efficacy profile was consistent across relevant subpopulations.

Within dex MR treatment groups, no clinically meaningful differences in healing rates were observed between subgroup levels (e.g., males vs. females in the dex MR 60-mg treatment group) for each of the demographic factors.

(b) (4) (dexlansoprazole)

The following table presents the primary efficacy findings stratified by age, race, gender, and BMI subgroups.

**Table 19: Crude Healing Rates at Week 8 for Selected Subgroups  
 (Integrated Analysis of Studies -084 & -085)**

Factor Category	Dexlansoprazole MR		Lansoprazole	p-value <sup>a</sup>		
	60 mg QD (N=1296) % [95% CI]	90 mg QD (N=1286) % [95% CI]	30 mg QD (N=1304) % [95% CI]	Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	Dex MR 60 mg vs Dex MR 90 mg
<b>Age (years) as strata</b>				0.007#	(b) (4)	
<45	(n=487) 84.6 [81.1, 87.7]	(b) (4)	(n=557) 78.3 [74.6, 81.6]			
45-<65	(n=659) 87.1 [84.3, 89.6]	(b) (4)	(n=618) 83.7 [80.5, 86.5]			
≥65	(n=150) 86.7 [80.2, 91.7]	(b) (4)	(n=129) 87.6 [80.6, 92.7]			
<b>Race as strata</b>				0.003#		
Caucasian	(n=1136) 85.5 [83.3, 87.5]	(b) (4)	(n=1135) 81.0 [78.6, 83.2]			
Black	(n=62) 95.2 [86.5, 99.0]	(b) (4)	(n=58) 96.6 [88.1, 99.6]			
Other	(n=98) 87.8 [79.6, 93.5]	(b) (4)	(n=111) 82.0 [73.6, 88.6]			
<b>Gender as strata</b>				0.003#		
Male	(n=715) 85.2 [82.4, 87.7]	(b) (4)	(n=696) 77.6 [74.3, 80.6]			
Female	(n=581) 87.3 [84.3, 89.0]	(b) (4)	(n=608) 86.5 [83.5, 89.1]			
<b>BMI (kg/m<sup>2</sup>) as strata</b>				0.003#		
<25	(n=269) 85.9 [81.1, 89.8]	(b) (4)	(n=250) 81.2 [75.8, 85.8]			
25-<30	(n=470) 84.7 [81.1, 87.8]	(b) (4)	(n=505) 82.8 [79.2, 86.0]			
≥30	(n=545) 87.7 [84.7, 90.3]	(b) (4)	(n=540) 81.1 [77.6, 84.3]			

Source: Table 2.7.x, p.64, Module 2.7.3, NDA 22-287

**Medical Officer Comments:**

Similar results are seen in the integrated analysis for the other subgroups mentioned above. Overall, it appears that the subgroup analysis for this primary endpoint:

1. confirms the results seen in the ITT population (significant differences seen between treatment groups and comparator for all subgroups); and,
2. does not reveal any imbalance to indicate that any one subgroup is driving the efficacy results (treatment response rates are similar between male and female, smoker and non-smoker, etc.)

Clinical Review  
Keith B. St. Amand, MD  
NDA 22-287  
**(b) (4)** (dexlansoprazole)

### 6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

In the Phase 1 studies, the pharmacodynamic profile of dex MR was assessed by measuring intragastric pH. The dex MR doses evaluated in Studies T-EE04-084 and T-EE04-085 were chosen based on results from 2 Phase 1 PK/PD studies (Studies T-P104-071 and T-P105-122).

In order to evaluate the relationship between plasma exposure of dex and the pharmacological response, the mean 24-hour intragastric pH, the percentage of time pH was >4.0, and AUC values following oral administration of dex MR 30 mg, 60 mg, 90 mg, and 120 mg from Studies T-P104-071 and T-P105-122 were combined. Estimates from exposure-response analyses indicated that dex MR doses ranging from 30 to 90 mg would result in gastric acid suppression similar to or higher than that typically observed for lansoprazole. Doses of dex MR 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; therefore, dex MR doses of 60 and 90 mg were selected to be included in the Phase 3 healing of EE studies.

#### Medical Officer Comments:

**The approach outlined above is rational from a biopharmaceutical perspective, and the clinical efficacy results as discussed above appear to support the choice of dose in that they demonstrated non-inferiority when compared to lansoprazole. However, as discussed at length in Section 6.1.4 above, the doses chosen did not show any clinically meaningful treatment difference over currently available therapy.**

### 6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of healing and/or tolerance effects were assessed in the 6-month maintenance of healed EE studies and will be discussed in Section 6.2 of this review.

### 6.1.9 Additional Efficacy Issues/Analyses

#### Medical Officer Comments:

**The sponsor's proposed indication includes the following language: "Healing (b) (4) (b) of all grades of erosive esophagitis." Although the reviewer believes the sponsor has demonstrated adequate evidence of dexlansoprazole's efficacy in healing of all grades of erosive esophagitis (b) (4)**

**(b) (4)**

**(b) (4)**

**For this reason, the reviewer believes that the indication should be changed to "healing of all grades of erosive esophagitis."**

Clinical Review  
Keith B. St. Amand, MD  
NDA 22-287  
(b) (4) dexlansoprazole)

## 6.2 Maintenance of healing of erosive esophagitis (MHEE)

The second indication sought by the sponsor for this application is for “maintaining healing of erosive esophagitis (b) (4) [redacted]”. The sponsor is seeking approval for (b) (4) [redacted] 30 mg (b) (4) [redacted] of dex daily for this indication.

### 6.2.1 Methods

#### 6.2.1.1 Overview of Study Design

Two studies were performed as follows:

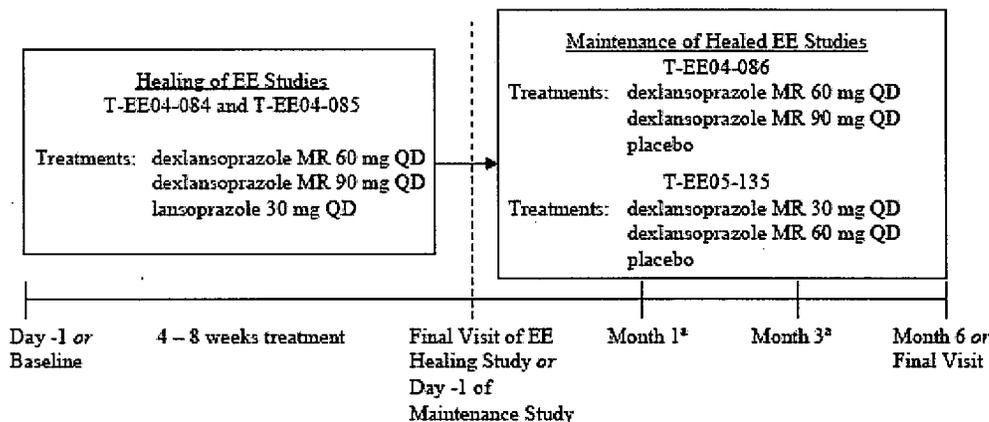
- Study T-EE05-135, which was a randomized, placebo-controlled, double-blind, multicenter trial comparing 3 arms: dexlansoprazole 60 mg daily, dexlansoprazole 30 mg daily, and placebo for 6 months
- Study T-EE04-086, which was also a randomized, placebo-controlled, double-blind, multicenter trial comparing 3 arms: dexlansoprazole 60 mg daily, dexlansoprazole 90 mg daily, and placebo for 6 months

These were both 6-month extension studies designed to evaluate maintenance of healed EE in subjects from 2 previous studies, T-EE04-084 and T-EE04-085, which evaluated endoscopic healing of EE. Enrollment in these studies required that subjects had already achieved endoscopically-proven healed EE in the short-term healing studies.

During the 6-month Treatment Period, subjects self-administered study drug orally QD before breakfast. Subjects documented the daily presence and maximum severity of daytime and nighttime heartburn symptoms and use of rescue medication throughout the study via a twice-daily diary. Subjects returned for study visits after 1, 3, and 6 months of treatment, and underwent various procedures at each visit, including an endoscopy. Subjects who showed recurrence of EE by endoscopy at any visit were discontinued from study drug.

The figure below illustrates the process by which patients were enrolled in the MHEE studies following their participation in the HEE studies.

**Figure 3: Schematic of HEE and MHEE Studies**



Source: Figure 2.7.3.2.a., p.24, Module 2.7.3, NDA 22-287

**Medical Officer Comments:**

It is appropriate to enroll subjects who have completed the healing of EE studies when seeking a claim for “maintenance of healing of EE.” However, it is interesting to note that those patients who achieved healing of their EE on lansoprazole in the HEE studies were re-randomized to treatment with dex or placebo in the MHEE studies. These patients are thus establishing dexlansoprazole’s efficacy in maintaining healing of EE even though they did not use the product to achieve their initial healing.

The reviewer does not feel this compromises the analysis of the efficacy of dex for the MHEE indication, however. In fact, it is clinically useful to evaluate the ability of dex to maintain healing in patients who took lansoprazole to achieve healing of their EE, since such switching between products occurs in clinical practice.

The following table presents more detailed information regarding number and location of study sites, study objectives and endpoints, and number of subjects by arm. (More detailed discussion of endpoints will follow later in this section.)

**Table 20: Description of Controlled Clinical Efficacy Studies for MHEE**

Study ID	Study Status	Number of Study Sites <sup>a</sup>	Study Design	Study Objectives			Endpoints <sup>b</sup>
Study Location(s)	Date of Study Start/Completion	Overall Enrollment Actual/Planned	Control Type				
T-EE03-133	Complete	94	Randomized, double-blind, placebo-controlled	To assess the efficacy in maintenance of healing and safety of dexlansoprazole MR (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 MR (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.			Efficacy: The percentage of subjects who maintained healed EE over 6 months as assessed by endoscopy.  Safety: Adverse events, physical examination, clinical laboratory values, fasting serum gastrin levels, gastric biopsies, and vital signs.
United States, Australia, Canada, the Czech Republic, Estonia, India, Latvia, Lithuania, Poland, and Slovakia	May-06/May-07	445/450	Placebo				
	<b>Study and Control Drugs Dose, Route, Regimen</b>	<b>Subjects by Arm Entered/Completed<sup>c</sup></b>	<b>Gender M/F</b>	<b>Median Age (Range)</b>	<b>Duration of Treatment</b>	<b>Study Population and Primary Inclusion Criteria</b>	
	30 mg oral dexlansoprazole MR QD 60 mg oral dexlansoprazole MR QD oral placebo QD	140/92 158/104 147/25	69/71 74/84 72/75	49.5 (21-85) 49.0 (22-78) 50.0 (18-84)	6 months	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-EE04-086	Complete	105	Randomized, double-blind, placebo-controlled	To assess the efficacy in maintenance of healed EE and safety of dexlansoprazole MR (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 MR (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.			Efficacy: The percentage of subjects who maintained healed EE over 6 months as assessed by endoscopy.  Safety: Adverse events, physical examination, clinical laboratory values, fasting serum gastrin levels, gastric biopsies, and vital signs.
United States	Jan-06/Nov-06	451/450	Placebo				
	<b>Study and Control Drugs Dose, Route, Regimen</b>	<b>Subjects by Arm Entered/Completed<sup>c</sup></b>	<b>Gender M/F</b>	<b>Median Age (Range)</b>	<b>Duration of Treatment</b>	<b>Study Population and Primary Inclusion Criteria</b>	
	60 mg oral dexlansoprazole MR QD 90 mg oral dexlansoprazole MR QD oral placebo QD	159/110 152/103 140/17	83/76 82/70 70/70	49.0 (20-81) 51.0 (19-83) 48.0 (19-81)	6 months	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.	

Source: Table 2.7.3.2.a., p.21-22, Module 2.7.3., NDA 22-287

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6.2.1.2 Eligibility Criteria