This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

2 Synopsis

<table>
<tr><td colspan="2">Name of Company: TAP Pharmaceutical Products Inc
Name of Finished Product: Dexlansoprazole MR Capsules
Name of Active Ingredient: (+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole</td></tr>
<tr><td colspan="2">Title of Study: A Phase 3 Study to Evaluate the Efficacy and Safety of Dexlansoprazole MR (60 mg QD and 90 mg QD) and an Active Comparator, Lansoprazole (30 mg QD), on Healing of Erosive Esophagitis</td></tr>
<tr><td colspan="2">Investigators: 153 investigators</td></tr>
<tr><td colspan="2">Study Centers: 150 sites (95 sites in the United States (US) and 55 sites throughout Australia, Bulgaria, Canada, Czech Republic, Estonia, Germany, India, Israel, Latvia, Lithuania, New Zealand, Poland, Russia, Slovakia, South Africa, and Ukraine)</td></tr>
<tr><td colspan="2">Publication (Reference): None</td></tr>
<tr><td>Study Period:
Date of First Dose: 02 December 2005
Date of Last Procedure: 30 January 2007</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="2">Objectives: The primary objectives were: (1) To assess the efficacy of dexlansoprazole modified release (MR) (TAK-390MR) 60 mg once daily (QD) and 90 mg QD compared to lansoprazole delayed-release capsules 30 mg QD in healing erosive esophagitis (EE) over 8 weeks in subjects with endoscopically proven EE and (2) To assess the safety 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: (1) 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 (2) 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 8 weeks in subjects with endoscopically proven moderate or severe EE.</td></tr>
<tr><td colspan="2">Methodology: Subjects with endoscopically proven EE were enrolled in this Phase 3, randomized, double-blind, multicenter, active-controlled, 3-arm, 8-week study. The study consisted of 2 periods: a Screening Period, and a Treatment Period, which lasted up to 8 weeks. Subjects who were eligible for entry into the Treatment Period were randomized in a 1:1:1 ratio to receive one of the following treatments: dexlansoprazole MR 60 mg QD, dexlansoprazole MR 90 mg QD, or lansoprazole 30 mg QD. Open-label Gelusil (North and South American sites) or an equivalent antacid (sites outside North and South America) was provided as a rescue medication for relief of heartburn, acid indigestion, and symptoms of gas.

During the 8-week Treatment Period, subjects self-administered one capsule of blinded study drug once daily in the morning before breakfast and returned for study visits after 4 and 8 weeks of treatment. If the subject's EE was healed at the Week 4 Visit, the subject completed the study with the Final Visit procedures. If the subject's EE was not healed at the Week 4 Visit, the subject remained in the study and took another 4 weeks of study drug. During both the Screening and Treatment Periods, subjects used an electronic or paper diary to document the daily presence and maximum severity of daytime and nighttime heartburn symptoms and usage of rescue medication throughout the study.</td></tr>
<tr><td colspan="2">Number of Subjects (Planned and Analyzed): 1950 subjects were planned, 2038 were enrolled.</td></tr>
<tr><td colspan="2">Diagnosis and Main Criteria for Inclusion: Male and female subjects who were 18 years of age or older with endoscopically proven EE.</td></tr>
<tr><td colspan="2">Duration of Treatment: Subjects received dexlansoprazole MR 60 mg QD, dexlansoprazole MR 90 mg QD, or lansoprazole 30 mg QD for up to 8 weeks.</td></tr>
</table>

Test Product, Dose and Mode of Administration, and Lot Numbers:

Test Product	Formulation	Dosage	Mode of Administration	Manufacturer	Drug Product Lot Number
Dexlansoprazole MR	One 60 mg capsule	60 mg QD	Oral	Takeda Pharmaceutical Co Ltd	[redacted]
Dexlansoprazole MR	One 90 mg capsule	90 mg QD	Oral	Takeda Pharmaceutical Co Ltd	[redacted]

Reference Therapy, Dose and Mode of Administration, and Lot Numbers:

Test Product	Formulation	Dosage	Mode of Administration	Manufacturer	Drug Product Lot Number
Lansoprazole Delayed-Release	One 30 mg capsule	30 mg QD	Oral	Takeda Pharmaceutical Co Ltd	[redacted]

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the percentage of subjects who had complete healing of EE over 8 weeks as assessed by endoscopy. The secondary efficacy variables were (1) the percentage of subjects who had complete healing of EE over 4 weeks as assessed by endoscopy and (2) the percentage of subjects with baseline EE Grade C or D (moderate or severe) who had complete healing of EE over 8 weeks as assessed by endoscopy.

Safety:

Safety was assessed through analysis of physical examinations, vital signs, and clinical laboratory tests and serum gastrin results, prior and concomitant medication assessment, gastric biopsy at baseline, and reported adverse events. All randomized subjects who received at least one dose of study drug were included in the safety analyses.

Statistical Methods:

Efficacy:

As prespecified in the protocol and original Statistical Analysis Plan (SAP), the primary analysis for the primary and secondary efficacy endpoints was to be based on the life table method, and for those endpoints, crude rate analysis was considered as supportive. Per request from the FDA at the Pre-NDA Meeting on 01 October 2007, the primary analysis for the primary and secondary efficacy endpoints was changed to crude rate analysis and analysis based on life table methods is now considered supportive.

The primary endpoint was assessed using a closed testing procedure by first assessing noninferiority of the dexlansoprazole MR doses to lansoprazole. Those dexlansoprazole MR doses shown to be noninferior to lansoprazole were then tested for superiority to lansoprazole. Since 2 doses of dexlansoprazole MR were being evaluated, control of the overall significance level at 0.05 was accomplished using Hochberg's method for multiple comparisons.

For those dexlansoprazole MR doses shown to be noninferior to lansoprazole, the 2 secondary efficacy endpoints were then assessed for superiority to lansoprazole. To maintain an overall significance level of 0.05, adjustments for multiplicity were made for 2 secondary efficacy endpoints using Hommel-Simes method within treatment group and for the number of dose comparisons using Hochberg's method per secondary efficacy endpoint.

The noninferiority assessment of the primary efficacy endpoint (proportion of subjects with healed EE by Week 8) was determined by calculating 95% confidence intervals (CI) for the difference between the crude healing rates of each dexlansoprazole MR dose and that of lansoprazole 30 mg. If the lower bound of that CI was greater than -10%, noninferiority was concluded. Superiority of primary and secondary efficacy endpoints was assessed by comparing the crude healing rate of each dexlansoprazole MR dose to that of lansoprazole 30 mg using a Cochran-Mantel-Haenszel (CMH) test with baseline LA EE Grade as strata.

Statistical Methods:
Efficacy (Cont):
Supportive analyses of the primary and secondary endpoints were performed using life table methods. Noninferiority was supported if the lower bound of the 95% CI for the difference with lansoprazole 30 mg of the estimated 8-week healing rate was greater than -10%. Superiority assessments for the primary and secondary efficacy endpoints were evaluated based upon the log-rank tests comparing treatments for the endpoints.

Safety:
Treatment-emergent adverse events were summarized by treatment group using the Medical Dictionary for Regulatory Agencies (MedDRA) coding dictionary. Comparisons between the treatment groups were made using Fisher's exact test. Laboratory values (including serum gastrin), vital signs values, and mean change from baseline values at each appropriate visit were summarized by treatment group. An overall comparison of the mean change from baseline between the treatment groups at each visit was made using a one-way analysis of variance (ANOVA) with treatment group as the factor and pairwise comparisons between all treatment groups were made using contrast statements within the framework of the ANOVA model.

Potentially clinically important (PCI) laboratory and vital signs values were summarized by treatment group, and comparisons between the treatment groups were made using Chi-square and Fisher's exact tests. Analyses of elevations in liver function tests and shifts in laboratory values from the normal ranges were also performed.

Summary and Conclusions:
Baseline Demographics:
No statistically significant differences were observed among treatment groups for any baseline demographic characteristics. Baseline demographic characteristics for all subjects are summarized in the following table:

Variable	Dexlansoprazole MR 60 mg QD (N=680)	Dexlansoprazole MR 90 mg QD (N=668)	Lansoprazole 30 mg QD (N=690)
Gender: n (%)			
Male	380 (55.9)	366 (54.8)	365 (52.9)
Female	300 (44.1)	302 (45.2)	325 (47.1)
Ethnicity: n (%)			
Hispanic or Latino	60 (8.8)	52 (7.8)	54 (7.8)
Not Hispanic or Latino	620 (91.2)	616 (92.2)	636 (92.2)
Race: n (%)			
American Indian or Alaskan Native	6 (0.9)	4 (0.6)	7 (1.0)
Asian	27 (4.0)	33 (4.9)	33 (4.8)
Black	32 (4.7)	33 (4.9)	27 (3.9)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0	1 (0.1)
White	602 (88.5)	580 (86.8)	601 (87.1)
Multiracial	10 (1.5)	15 (2.2)	17 (2.5)
Age (years): n (%)			
<45	269 (39.6)	276 (41.3)	288 (41.7)
45 to <65	349 (51.3)	328 (49.1)	332 (48.1)
≥65	62 (9.1)	64 (9.6)	70 (10.1)
Mean±SD	47.8±13.71	47.3±13.93	47.3±13.74
Median	49.0	48.0	47.0
Min-Max	18-84	18-85	18-87
Baseline LA Classification Grade: n (%)			
A	236 (34.7)	242 (36.2)	231 (33.5)
B	247 (36.3)	233 (34.9)	248 (35.9)
C	163 (24.0)	148 (22.2)	170 (24.6)
D	33 (4.9)	45 (6.7)	40 (5.8)
NA	1 (0.1)	0	1 (0.1)

Summary and Conclusions (Cont):

Efficacy Results:

The results of this study demonstrated noninferiority of both dexlansoprazole MR 60 mg QD and 90 mg QD to lansoprazole 30 mg QD for the healing rates by Week 8 (crude rate analysis). In addition, both dexlansoprazole MR 60-mg QD and 90-mg QD doses were statistically significantly superior to lansoprazole 30 mg QD in Week 8 healing rates with approximately 6% and 7% therapeutic gains, respectively. From the preplanned analysis for the healing rates estimated by life table method, both doses were noninferior and statistically significant superiority was nearly reached for both dexlansoprazole MR treatment groups. Dexlansoprazole MR 60 mg QD (p=0.060) did not reach the statistical significance level of 0.05, and dexlansoprazole 90 mg QD (p=0.029) did not reach the statistical significance level of 0.025 required by Hochberg's multiplicity adjustment (both p-value ≤0.05 or one p-value ≤0.025), which was used to maintain a nominal significance level of 0.05.

Week 8 Healing Rate/ Analysis	Dexlansoprazole MR		Lansoprazole	p-value		
	60 mg QD % (95% CI)	90 mg QD % (95% CI)	30 mg QD % (95% CI)	Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	Dex MR 60 mg vs Dex MR 90 mg
Crude (Primary)[a]	(N=639)	(N=634)	(N=656)	0.004#	0.001#	0.727
	85.3 (82.3, 87.9)	85.8 (82.8, 88.4)	79.0 (75.6, 82.0)			
Life Table (Supportive)[b]	(N=673)	(N=665)	(N=684)	0.060	0.029	0.707
	92.3 (90.0, 94.7)	92.2 (89.8, 94.6)	86.1 (83.0, 89.2)			

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

a p-values are from CMH test with baseline EE Grade as strata.

b p-values are from log-rank tests using day as a discrete time unit.

Dexlansoprazole MR treatment group is statistically significantly superior to lansoprazole using Hochberg's method at a nominal significance level of 0.050.

Based on the primary analysis using crude healing rates, dexlansoprazole MR 60 mg QD was statistically superior to lansoprazole 30 mg QD for healing of the more severe grades of EE (LA Grades C or D combined) after an 8-week treatment period and showed a therapeutic gain of 15 percentage points. Dexlansoprazole 90 mg QD showed a therapeutic gain of 9 percentage points; however, it was not statistically superior to lansoprazole 30 mg QD (p=0.045) due to the Hommel-Simes' multiplicity adjustment for the 2 secondary efficacy endpoints.

Week 8 for C/D Healing Rate/ Analysis	Dexlansoprazole MR		Lansoprazole	p-value		
	60 mg QD % (95% CI)	90 mg QD % (95% CI)	30 mg QD % (95% CI)	Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	Dex MR 60 mg vs Dex MR 90 mg
Crude (Primary)[a]	(N=182)	(N=185)	(N=200)	0.002#	0.045	0.245
	79.7 (73.1, 85.3)	74.1 (67.1, 80.2)	65.0 (58.0, 71.6)			
Life Table (Supportive)[b]	(N=191)	(N=191)	(N=208)	0.011#	0.017#	0.927
	88.9 (83.7, 94.2)	83.8 (77.4, 90.1)	74.5 (67.3, 81.6)			

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

Statistical significances of the tests for the 2 secondary efficacy endpoints when comparing dexlansoprazole MR doses to lansoprazole were determined by applying Hommel-Simes method within treatment and also by Hochberg's method for treatment comparisons for each endpoint. Although unadjusted p-values are displayed, after applying both adjustments to the p-values, the significance at a nominal 0.05 level is indicated.

a p-values are from CMH test with baseline EE Grade as strata.

b p-values are from log-rank tests using day as a discrete time unit.

Summary and Conclusions:

Efficacy Results (Cont):

Healing rates by Week 4 based on the crude rate analysis were similar among treatment groups (66.2%, 68.8%, and 64.8% for the dexlansoprazole MR 60 mg QD, dexlansoprazole MR 90 mg QD, and lansoprazole 30 mg QD treatment groups, respectively).

These 2 secondary efficacy endpoints were also analyzed by the prespecified life table method. Both dexlansoprazole MR 60 mg QD and 90 mg QD were statistically significantly superior to lansoprazole 30 mg QD for healing of the more severe grades of EE (baseline LA EE Grades C or D) over 8 weeks of treatment. The therapeutic gains over lansoprazole 30 mg QD of approximately 14 percentage points for dexlansoprazole MR 60 mg QD and 9 percentage points for dexlansoprazole MR 90 mg QD in healing moderate to severe EE. The results for the other secondary efficacy endpoint, healing rates by Week 4 by the life table method, were similar among the treatment groups (77.0%, 78.8%, and 76.5% in the dexlansoprazole MR 60 mg QD, dexlansoprazole MR 90 mg QD, and lansoprazole 30 mg QD treatment groups, respectively).

Safety Results:

In this study of subjects with endoscopically proven EE, dexlansoprazole MR in doses of 60 mg QD and 90 mg QD for up to 8 weeks was generally well tolerated. The most frequently reported (≥4% of subjects in any treatment group by MedDRA HLT) treatment-emergent adverse events were Diarrhoea (Excl Infective), Gastrointestinal and Abdominal Pains (Excl Oral and Throat), and Upper Respiratory Tract Infections. No statistically or clinically significant differences were observed among the treatment groups for ≥1% of subjects reporting treatment-emergent adverse events in any Medical Dictionary for Regulatory Activities (MedDRA) High Level Term (HLT). The percentage of subjects who experienced treatment-related adverse events was not statistically significantly different among treatment groups and did not exceed 3% in any treatment group. No dose-related trends were observed in adverse events. Thirty-five subjects reported adverse events as the primary reason for premature discontinuation from the study. In addition to 2 deaths, 11 subjects reported treatment-emergent serious adverse events (SAEs) (4 in the dexlansoprazole MR 60 mg QD treatment group, 2 in the dexlansoprazole MR 90 mg QD treatment group, and 5 in the lansoprazole 30 mg QD treatment group). The investigators assessed the 2 deaths (one subject in the dexlansoprazole MR 60 mg QD treatment group and one subject in the lansoprazole 30 mg QD treatment group) and all other SAEs as not related to study drug, with the exception of one possibly related SAE (MedDRA PT: Hemiparesis) in the lansoprazole 30 mg QD treatment group. No clinically significant differences were observed in the percentage of subjects with shifts to outside the normal range for clinical laboratory parameters in the dexlansoprazole MR treatment groups compared to the lansoprazole treatment group.

Statistically significant differences were observed in serum gastrin levels in the dexlansoprazole MR treatment groups compared to the lansoprazole 30 mg QD treatment group. Barrett's esophagus was suspected during treatment in a total of 33 subjects who were similarly distributed across the 3 treatment groups and were not suspected of having Barrett's esophagus during screening.

Conclusions:

Dexlansoprazole MR 60 mg and 90 mg QD were highly effective for healing of EE and were statistically significantly superior to lansoprazole 30 mg QD for the Week 8 crude healing rates. In addition, dexlansoprazole MR 60 mg QD achieved statistically significant superiority to lansoprazole 30 mg QD for healing of the more severe grades of EE by Week 8. Overall and in more severe grades of EE, both dexlansoprazole MR doses provided clinically meaningful therapeutic benefit relative to lansoprazole 30 mg QD for healing by Week 8. All 3 treatments were effective in relieving heartburn. Dexlansoprazole MR in doses of 60 mg QD and 90 mg QD for up to 8 weeks of treatment was generally well tolerated by subjects with EE and demonstrated a comparable safety profile to that of lansoprazole 30 mg QD in this study.

Date of Report: 19 October 2007