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Clinical Trial Synopsis C02-039, NCT# 00175045

Name of Company: TAP Pharmaceutical Products Inc.

Name of Finished Product: Prevacid[®] (lansoprazole) **Name of Active Ingredient:** 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole

Title of Study: A Phase 2, Open-Label Multicenter Study to Evaluate the Pharmacodynamics of Intravenous Lansoprazole to that of Oral Lansoprazole in Subjects with Erosive Esophagitis

Investigators who Enrolled Subjects: Six investigators at separate sites participated in the study.

Study Centers that Enrolled Subjects: Multicenter - United States

Publication (Reference):

Metz DC, Cong H, Chang L. Intravenous lansoprazole is equivalent to oral capsule in suppressing pentagastrin-stimulated acid output. *American College of Gastroenterology Annual Scientific Meeting*. American College of Gastroenterology. *Am J Gastroenterol*. 2004; 99(Suppl); S14. Abstract 37. Abstract Number 37. ACG Annual Scientific Meeting 2004. TAP-08-000322

Study Period:

Study Initiation Date: 24 June 2003
Study Completion Date: 29 October 2003

Phase of Development: 2

Objective: The objective of this study was to compare the pharmacodynamics (PD) of intravenous (IV) lansoprazole 30 mg to oral (PO) lansoprazole 30 mg capsules in subjects with erosive esophagitis.

Methodology: This was a Phase 2, open-label, multicenter, 2-period study to compare the PD of IV lansoprazole 30 mg (delivered in 30 minutes) to oral lansoprazole 30 mg in subjects with erosive (Grade ≥ 2) esophagitis diagnosed by endoscopy. Subjects completed all pretreatment procedures in the 2 weeks before receiving study drug. During the first period of study drug exposure, oral lansoprazole 30 mg was administered once daily (QD) to each subject one hour before the morning meal on 7 successive days, while during the second period, IV lansoprazole 30 mg was administered to each subject as a 30-minute infusion 1 hour before the morning meal on 7 successive days. On 3 occasions during the study, gastric contents were collected from each subject to determine basal acid output (BAO) and pentagastrin-stimulated maximum acid output (MAO). The BAO and MAO measurements were obtained 21 hours and 22 hours, respectively, following the last dose of study drug on Treatment Period 2 Day 1 (after the last oral dose), on Treatment Period 2 Day 2 (after the first IV dose), and on Posttreatment Day 1 (after the last IV dose).

Safety of study drug was monitored through assessments of adverse events (AEs), concomitant medication use, vital signs, physical examinations, laboratory evaluations, pregnancy testing, 12-lead electrocardiograms (ECGs), ophthalmic examination (visual acuity and fundoscopic examination), and IV injection sites.

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Number of Subjects (Planned and Analyzed): The study protocol specified that approximately 64 subjects should be enrolled. Sixty-eight subjects were enrolled in the study and were analyzed for safety; 59 subjects were included in the PD analysis.

Diagnosis and Main Criteria for Inclusion: All study subjects were required to have erosive (Grade 2, 3, or 4) esophagitis according to the TAP Grading Scale as determined during the pretreatment endoscopy, and to test negative for *Helicobacter pylori* (*H pylori*).

Duration of Treatment: Once daily for 14 days (7 days oral followed by 7 days IV)

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:			
Test Product	Dose	Mode of Administration	Lot Number
Lansoprazole for injection	30 mg	Intravenous	Z3387371

Reference Therapy, Dose and Mode of Administration, Lot Number:			
Reference Product	Dose	Mode of Administration	Lot Number
Lansoprazole capsule	30 mg	Oral	ONNK504

Criteria for Evaluation:

Efficacy

Not applicable. This study was not designed to evaluate efficacy; surrogate endpoints are listed under Pharmacodynamics.

Pharmacodynamics

The primary PD variable was the MAO obtained 22 hours after the last dose of IV lansoprazole compared to the MAO obtained 22 hours after the last dose of oral lansoprazole following pentagastrin stimulation in both instances.

The secondary PD variables included the BAO results obtained 21 hours after the last dose of IV lansoprazole compared with that obtained 21 hours after the last dose of oral lansoprazole. Additional PD parameters included the BAO and MAO results obtained 21 hours and 22 hours, respectively, after the first dose of IV lansoprazole versus those obtained after the last dose of oral lansoprazole, as well as the BAO and MAO results obtained after the first versus last dose of IV lansoprazole.

Safety

Safety evaluations included AE assessments, injection site assessments, physical examinations, 12-lead ECGs, pregnancy testing, vital signs, clinical laboratory determinations, ophthalmic examinations (visual acuity and fundoscopic examinations), and use of concomitant medications.

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Statistical Methods:

Efficacy

See Pharmacodynamics.

Pharmacodynamics

The BAO and MAO data obtained on Days 1 and 2 of Treatment Period 2 and on Posttreatment Day 1 were summarized using descriptive statistics including mean, standard deviation, and quartiles. Comparisons were made between the MAO measurements (primary variable) obtained after the last IV dose and the last oral dose, and between the BAO measurements (secondary variable) after those doses. If the ratio of the population average for IV lansoprazole to that of oral lansoprazole were less than 120%, the 2 dosage forms would be considered pharmacodynamically equivalent. The null hypothesis of the test was specified as the population average of MAO and BAO for IV lansoprazole minus 120% of the MAO and BAO for oral lansoprazole being non-negative (ie, $IV - 1.2 \times PO \geq 0$). Noninferiority would be concluded if the null hypothesis were rejected at a significance level of 0.05.

Safety

All subjects who were enrolled into the study and took at least 1 dose of study drug were included in the safety analyses. The numbers and percentages of subjects who reported AE(s) were tabulated by System Organ Class, High Level Term, and Preferred Term using Medical Dictionary for Regulatory Activities (MedDRA) terminology and classification.

Summary/Conclusions:

Demographics:

Gender: Female 17 (25%), Male 51 (75%);

Race: Black 5 (7%), White 57 (84%), Hispanic: 5 (7%); Other: 1 (2%).

Age 42.7 ± 13.4 (range 19 to 72) years;

Weight: 198.9 ± 42.8 (92 to 292) lbs;

Height: 68.9 ± 4.2 (59-76) in.

Efficacy Results

See Pharmacodynamic Results.

Pharmacodynamic Results

The primary PD variable was the MAO measured after the last dose of IV lansoprazole 30 mg as compared to that after the last dose of oral lansoprazole 30 mg capsule. After 7 days of treatment with oral lansoprazole 30 mg capsule QD, the median MAO was 7.72 mEq/hour among the 58 subjects with available data. After the subjects were then treated with IV lansoprazole 30 mg for 7 days, the median MAO was 7.25 mEq/hour among the 57 subjects with available data. The null hypothesis, specified as the population median being greater than or equal to 0 for MAO for IV lansoprazole minus 120% of MAO for oral lansoprazole [ie, $(\text{last } IV_{MAO}) - (1.2 \times \text{last } PO_{MAO}) \geq 0$], was rejected ($p=0.001$, $N=56$) at a level of significance of 0.05, thus establishing noninferiority of IV lansoprazole.

One of the secondary PD variables was the BAO measured after the last dose of IV lansoprazole 30 mg as compared to that after the last dose of oral lansoprazole 30 mg capsule. After 7 days of treatment with oral lansoprazole 30 mg capsule QD, the median BAO was 0.73 mEq/hour among the 59 subjects with available data. After the subjects were then treated with IV lansoprazole 30 mg for 7 days, the median BAO was 0.45 mEq/hour among the 57 subjects with available data. The null hypothesis, specified as the population median being greater than or equal to 0 for BAO for IV lansoprazole minus 120% of BAO for oral lansoprazole was rejected ($p=0.011$, $N=57$) at a level of significance of 0.05, thus establishing noninferiority of IV lansoprazole.

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Safety Results

Adverse events were reported by 49% (29/59) of subjects during the IV regimen and 37% (25/68) during the oral regimen. Adverse events that occurred most frequently in subjects during IV dosing included; Injection and Infusion Site Reactions (11/59; 19%), Nausea and Vomiting Symptoms (5/59; 8%), and Headaches Not Elsewhere Classified (NEC) (4/59; 7%). Adverse events that occurred most frequently in subjects during oral dosing included; Headaches NEC (8/68; 12%), Nausea and Vomiting Symptoms (4/68; 6%), and Neurological Signs and Symptoms NEC (4/68; 6%). Adverse events considered by the investigator to be treatment related were reported by 8% (5/59) of subjects during the IV regimen and 9% (6/68) during the oral regimen. The treatment-related AE that occurred most frequently in subjects during the period of IV dosing was Diarrhoea (Excl Infective) (2/59; 3%). Treatment-related AEs that occurred most frequently in subjects during oral dosing included Headaches NEC (3/68; 4%) and Neurological Signs and Symptoms NEC (2/68; 3%). All AEs were mild to moderate in severity. No serious adverse events, deaths, pregnancies, premature discontinuations (due primarily to AEs), or other significant AEs were reported during the study.

Date of Synopsis: 03 March 2008