

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-566

**Clinical Pharmacology and Biopharmaceutics
Review**

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-566
Brand Name: Prevacid®
Generic Name: Lansoprazole
Dosage Form and Strength: Lyophilized sterile powder for injection, 30 mg
Route of Administration: Intravenous
Indication: When the patients are unable to take the oral formulations, Prevacid I.V. for injection is indicated as an alternative for the short-term treatment (up to 7 days) of all grades of erosive esophagitis
Dosage and Administration: 30 mg lansoprazole per day administered by IV infusion 30 minutes for up to 7 days
Sponsor: TAP Pharmaceuticals Inc.
Type of Submission: Original
Clinical Division: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products)
OCPB Division: HFD-870/Division of Pharmaceutical Evaluation II
Priority: Standard
Submission Date: 12/20/02
Reviewer: Tien-Mien Chen, Ph.D.
Team leader: Suresh Doddapaneni, Ph.D.

I. Executive Summary

The pharmacokinetic (PK) and pharmacodynamic (PD) data submitted in support of this NDA came from four Clinical Pharmacology studies. Intravenous (IV) administration of lansoprazole 30 mg QD resulted in higher systemic exposure [higher peak plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) values] compared to that of oral lansoprazole 30 mg QD. Intravenous 30-minute infusion of lansoprazole 30 mg QD showed an improvement over oral route in gastric acid output suppression with respect to BAO (basal acid output), but not significantly different in terms of MAO (pentagastrin-stimulated maximum acid output) in patients on Day 7. Overall, equivalent dose of 30 mg lansoprazole administered by IV 30-minute infusion every day for 7 days produces similar gastric acid output suppression compared to oral lansoprazole.

A. Recommendations

From the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) perspective, NDA 21-566 for Prevacid® I.V. for Injection submitted on 12/20/02 is acceptable provided that the sponsor and Agency can come to a satisfactory agreement with respect to the language in the package insert. The Agency's CPB related labeling changes are contained in Appendix 1 (p. 9).

B. Phase IV commitments

None

*Appears This Way
On Original*

09/05/03

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Suresh Doddapaneni, Ph.D. _____

FT initialed by Suresh Doddapaneni, Ph.D. _____

II. Table of Contents

	Page
I. Executive Summary	1
II. Table of Contents	3
III. Summary of CPB Findings	3
IV. QBR	4
V. Detailed Labeling Recommendations	9
VI. Appendices	9

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Lansoprazole, a compound of the substituted benzimidazole class, inhibits gastric acid secretion by binding covalently to the parietal cell membrane enzyme (H^+ , K^+)-ATPase, or the proton pump. Three oral dosage forms of lansoprazole sponsored by TAP Pharmaceuticals are currently approved: delayed release 15 and 30 mg capsules (NDA 20-406), delayed release 15 and 30 mg/packet for suspension (NDA 21-281), and orally disintegrating 15 and 30 mg tablets (NDA 21-428). The approved indications for the oral products are: short-term treatment of active duodenal ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, maintenance of healed duodenal ulcers, short-term treatment of active benign gastric ulcer, healing of non-steroid anti-inflammatory drugs (NSAID)-associated gastric ulcer, risk reduction of NSAID-associated gastric ulcer, gastroesophageal reflux disease (GERD), short-term treatment of symptomatic GERD, short-term treatment of erosive esophagitis (EE), maintenance of healing of EE, and pathological hypersecretory conditions including Zollinger-Ellison syndrome. Prevacid I.V. for injection is specifically indicated for the short-term treatment (up to 7 days) of all grades of erosive esophagitis as an alternative when patients are unable to take oral formulations. Once the patient is able to take medication orally, therapy can be switched back to the oral route.

Two pivotal (M01-308 and M01-307) and two supportive (M95-306 and M96-486) clinical pharmacology studies were submitted in support of this NDA. The two pivotal studies were designed to demonstrate that gastric acid output suppression can be maintained in subjects who switched from oral to IV dosing of Prevacid 30 mg QD. Study M01-308 was conducted in adult patients with EE. Study M01-307 was conducted in healthy adult subjects. Studies M95-306 and M96-486 were conducted in healthy adult subjects to determine single- and multiple-dose PK and 24-hour intragastric pH values, respectively.

Regarding PK results, IV administration of lansoprazole 30 mg QD resulted in higher systemic exposure (higher C_{max} and AUC values) compared to that of oral QD dosing of lansoprazole 30 mg. For gastric acid output suppression on Day 7, IV 30-minute infusion of lansoprazole 30 mg QD showed an improvement over oral route with respect to BAO, but not significantly different in terms of MAO in patients. In healthy adults, IV lansoprazole was not significantly different from the oral lansoprazole with respect to both BAO and MAO.

Question Based Review

A. General Attributes

Four Clinical Pharmacology studies (M95-306, M96-486, M01-307, and M01-308) were submitted in support of this NDA. Separate clinical efficacy and safety studies were not conducted. Studies M95-306 and M96-486 were designed to evaluate PK and PD, i.e., 24-hr intragastric pH, in healthy volunteers for single and multiple doses of lansoprazole, respectively. On 12/22/2000, NDA 21-331 was submitted by TAP with data from these two studies. After discussions with FDA, TAP withdrew this NDA on 2/15/2001 due to the Agency's request to evaluate IV lansoprazole in patients. Subsequently, studies M01-307 and M01-308 were conducted to demonstrate that gastric acid output suppression could be maintained in subjects who were switched from oral to IV of lansoprazole 30 mg QD. Study M01-307 determined PK and PD (BAO and MAO) in healthy subjects while study M01-308 determined PD (BAO and MAO) in patients with EE.

B. General Clinical Pharmacology

Q 1. How does the IV PK and PD of lansoprazole compare to that of oral lansoprazole?

After equivalent doses of 30 mg, IV administration over 30 minutes resulted in higher systemic exposure (higher C_{max} [155% ↑] and AUC [35% ↑] values) compared to that of oral dosing. The IV and oral terminal half-lives, however, were similar. As with oral or IV dosing, little accumulation (<10%) of plasma lansoprazole levels was observed in healthy subjects after once a day multiple dosing to steady state. Thirty (30) mg and 60 mg of lansoprazole given by IV 30-minute infusion exhibited dose-proportionality. Relative to oral dosing, after lansoprazole 30 mg IV was administered over 30, 60, and 120 minutes, C_{max} decreased as the infusion time increased with similar AUC (Table 1) and intragastric pH values (Figure 1 and Table 2). The mean absolute bioavailability of Prevacid oral 30 mg capsule was determined to be about 70%.

Appears This Way
On Original

Table 1. Mean (\pm Standard Deviation) Lansoprazole Single-Dose PK Parameters (M95-306)

Regimen	Dose Administration				
	Oral 30 mg	30 mg over 30 min	30 mg over 60 min	30 mg over 120 min	60 min over 30 min
C_{max} (ng/mL)	682 (\pm 366)	1736 (\pm 471)	1346 (\pm 341)	934 (\pm 317)	3589 (\pm 725)
T_{max} (hr)	2.0 (\pm 1.1)	0.5 (\pm 0.1)	1.0 (\pm 0.1)	2.0 (\pm 0.2)	0.5 (\pm 0.1)
$AUC_{0-\infty}$ (ng-h/mL)	2300. (\pm 1851)	3103 (\pm 1941)	3163 (\pm 2120.)	3017 (\pm 2208)	7130. (\pm 4027)
$T_{1/2}$ (hr) [#]	1.2	1.1	1.1	1.1	1.2
CL (L/hr)	19.5* (\pm 10.5)	12.8 (\pm 6.1)	12.7 (\pm 5.7)	13.4 (\pm 5.9)	10.5 (\pm 4.2)
Vd_{ss} (L)	-----	17.7 (\pm 5.6)	17.5 (\pm 2.7)	20.6 (\pm 6.1)	16.3 (\pm 2.4)

[#] Harmonic mean.

* Calculated ad CL/F.

Figure 1. Mean Lansoprazole Plasma Concentration Time Profiles after Oral and IV Administrations

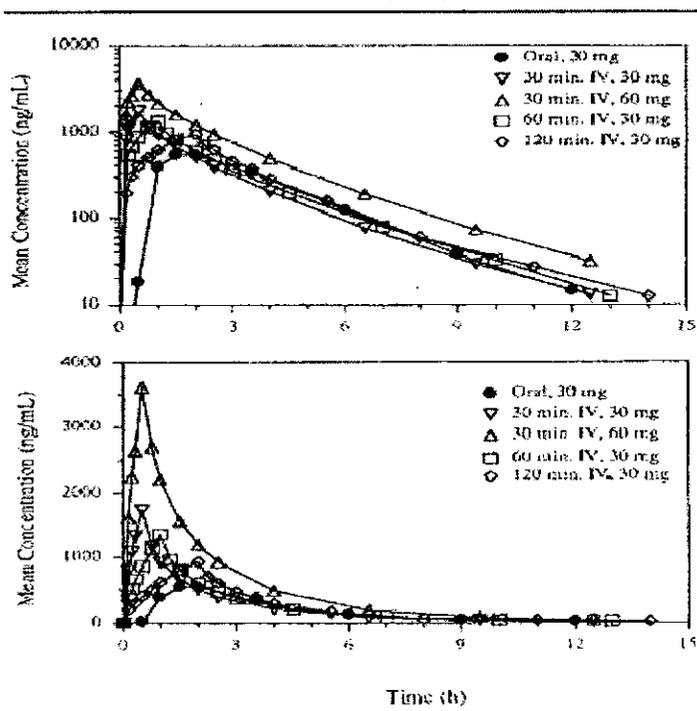


Table 2. Mean Intra gastric pH Values and Mean % of Time that the Intra gastric pH Values Above 3 and 4 During 24-hr Monitoring Period (M95-306)

Summary of pH Assessments (Single-Dose)				
Regimen				
	Oral 30 mg	IV 30 mg over 30 min	IV 30 mg over 60 min	IV 30 mg over 120 min
Mean 0-23 hour pH	3.16	3.39	3.59	3.44
% of time pH> 3	43.5	50.3	54.6*	51.8
4	32.9	36.8	41.3	39.4

*. Statistically significant difference compared to oral 30 mg (p<0.05).

After multiple dosing, IV lansoprazole 30 mg QD (Treatments C and D) also showed no significant difference (at p=0.05 level) from oral QD dosing (Treatment A) on Day 5 (Table 3 and Figure 2 below). Pharmacokinetics were not altered when lansoprazole was administered in either of the two vehicles, PEG 400 or 0.9% Sodium Chloride.

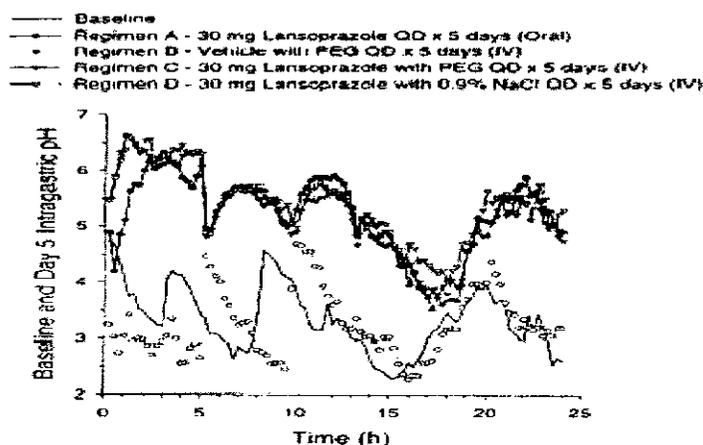
Table 3. Mean Intra gastric pH Values and Mean % of Time that the Intra gastric pH Values Above 3 and 4 During 24-hr Monitoring Period on Day 5 (M96-486)

Summary of pH Assessments (Day 5)					
Regimen					
	Baseline	A: Oral 30 mg	B: Vehicle Only (PEG)	C: IV 30 mg (in PEG) over 30 min	D: IV 30 mg (in 0.9% NaCl) over 30 min
Mean 0-24 pH	3.33	5.25*	3.28	5.27* [#]	5.36* [#]
% of time pH> 3	45.3	83.9*	44.1	85.6* [#]	85.5* [#]
4	31.1	77.6*	31.0	79.4* [#]	79.6* [#]

*. Statistically significant difference (p<0.05) found between active treatments and baseline.
#. No significant difference between IV (Treatments C and D) and oral (Treatment A).

Appears This Way
On Original

Figure 2. Mean Intra-gastric pH-Time profiles for Baseline and Treatments A-D on Day 5 (M96-486)



Q2. Was the gastric acid output suppression similar between oral and IV dosing of Prevacid 30 mg QD in patients and in healthy subjects ?

Overall, IV administration of 30 mg Prevacid QD is similar to oral route for maintaining the gastric acid output suppression thus supporting the proposed indication.

In patients, lansoprazole 30 mg QD given by IV 30-minute infusion for 7 days showed an improvement than oral dosing in terms of BAO. No significant difference was found with respect to MAO (Table 4).

Table 4. Summary of BAO and MAO Data Obtained from Oral and IV Dosing on Day 7 (M01-308)

	Lansoprazole 30 mg		p-Value*
	Oral (Day 7)	IV (Day 7)	
Median BAO	0.89 mEq/hr	0.51 mEq/hr	0.059
Median MAO	7.31 mEq/hr	7.64 mEq/hr	0.002

*p-Value: <0.05 represents the equivalency being established since null hypothesis that Oral (Day 7) and IV (Day 7) differed by more than 20% was rejected.

In addition, IV (Day 7) showed an improvement as compared to IV (Day 1) in terms of BAO data, however, no significant difference was found according to MAO data (Table 5) below.

Table 5. Summary of BAO and MAO Data Obtained from IV Dosing on Days 1 and 7 (M01-308)

	Lansoprazole 30 mg		p-Value*
	IV (Day 1)	IV (Day 7)	
Median BAO	0.64 mEq/hr	0.51 mEq/hr	0.314
Median MAO	8.19 mEq/hr	7.64 mEq/hr	<0.001

*p-Value: <0.05 represents the equivalency being established since null hypothesis that IV (Day 1) and IV (Day 7) differed by more than 20% was rejected.

In healthy subjects, BAO and MAO data indicated that equivalency was established (Tables 6 and 7).

Table 6. Summary of BAO and MAO Data Obtained from Oral and IV Dosing on Day 7 (M01-307)

	Lansoprazole 30 mg		p-Value*
	Oral (Day 7)	IV (Day 7)	
Median BAO	0.42 mEq/hr	0.27 mEq/hr	0.034
Median MAO	4.76 mEq/hr	5.13 mEq/hr	0.027

*p-Value: <0.05 represents the equivalency being established since null hypothesis that Oral (Day 7) and IV (Day 7) differed by more than 20% was rejected.

Table 7. Summary of BAO and MAO Data Obtained from IV Dosing on Days 1 and 7 (M01-307)

	Lansoprazole 30 mg		p-Value*
	IV (Day 1)	IV (Day 7)	
Median BAO	0.58 mEq/hr	0.27 mEq/hr	0.009
Median MAO	6.86 mEq/hr	5.13 mEq/hr	<0.001

*p-Value: <0.05 represents the equivalency being established since null hypothesis that IV (Day 1) and IV (Day 7) differed by more than 20% was rejected.

C. General Biopharmaceutics

Prevacid® I.V. for Injection is supplied as a sterile, lyophilized powder containing lansoprazole 30 mg, mannitol 60 mg, meglumine 10 mg, and sodium hydroxide 3.45 mg per vial. It is to be reconstituted with 5 mL of Sterile Water for Injection, USP and then

diluted in 50 mL of 0.9% Sodium Chloride Injection, USP for IV infusion over 30 minutes. The formulation to-be-marketed and that used in the clinical trials is the same.

D. Analytical Section

The assay method was reviewed and found to be satisfactory (Tables 8 and 9):

Table 8.

Study Number	Lansoprazole	Method	Standard Curve Range	LLOQ
M01-307	R-(+)	[(n=9)	ng/mL
	S(-)		(n=9)	ng/mL
M95-306	Racemate]	(n=9)	ng/mL [#]
M96-486	R-(+)		(n= 8)	ng/mL
	S(-)	(n= 8)	ng/mL	

Table 9.

Study Number	Assay Method Validation		Quality Control			
	Lansoprazole		Intraday Variation (%)	Interday Variation (%)	Recovery (%)	Coefficient of Variation (%)
M01-307	R-(+)	ng/mL (n=4)	[
	S(-)	ng/mL (n=4)				
M95-306	Racemate	ng/mL(n=3)]			
M96-486	R-(+)	ng/mL (n= 4)				
	S(-)	ng/mL (n= 4)				

V. Detailed Labeling Recommendations

Appendix I contains detailed CPB related labeling comments. Double underline represents "addition" (in blue) and double strikethrough represents "deletion" (in red).

VI. Appendices

1. Proposed Package Insert (Sponsor Proposed and OCPB Recommendations)
2. Individual Study Review
3. Cover Sheet and OCPB Filing/Review Form

Appendix 1

Proposed Labeling (version 04/10/03) with Agency's Comments

*Appears This Way
On Original*

17 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Appendix 2

Individual Study Reviews

*Appears This Way
On Original*

Study No. M01-307 (Vol. 1.19)

Summary

Title: The Pharmacokinetics and Pharmacodynamics of 30 mg Intravenous Lansoprazole and 30 mg Oral Lansoprazole in Healthy Subjects. (Protocol M01-307)

Objective: The objective of this study was to evaluate the pharmacokinetics, pharmacodynamics and safety of 30 mg intravenous lansoprazole and 30 mg oral lansoprazole in healthy subjects. This report presents only the pharmacokinetic aspects of the study.

Investigator and Study Dates: This study was conducted []
] The principal investigator was [] Subjects were
dosed between January 22, 2002 and March 11, 2002.

Demographic and Accountability: A total of 29 healthy adult subjects (24 males and 5 females) were enrolled in the study and 28 subjects completed the study. Of the 28 subjects who completed the study, 27 (96%) were Caucasian and one (4%) was Hispanic. The mean \pm SD values for age, body weight and height for the subjects were 29 ± 8.7 (range: 19 - 45) years, 79.6 ± 10.4 (range: 55.8 - 94.9) kg and 177.6 ± 9.8 (range: 156.2 - 193.0) cm, respectively.

Study Design and Dose Administration: This was a Phase I, open-label, single-center study to evaluate the pharmacokinetics and pharmacodynamics of lansoprazole in healthy subjects following the administration of 30 mg oral and intravenous doses of lansoprazole.

Subjects who completed the screening procedures and were eligible to enter the study received study drug as follows:

Best Possible Copy

Study Period	Study Days	Route of Administration (Dose/Day)	Formulation
Period 1	1-7	Oral (30 mg)	Lansoprazole capsules
Period 2	8-14	30-minute intravenous infusion (30 mg)	Lansoprazole in 0.9% NaCl

In order to assess the effect of changing the route of administration from oral to intravenous on the pharmacokinetics and pharmacodynamics of lansoprazole, there was no washout period. In each study period, lansoprazole doses were administered at 9:00 a.m. Gastric fluid samples were collected on Days -1, 8, 9, and 15 via a nasogastric tube in order to determine basal acid output (BAO) and pentagastrin-stimulated maximal acid output (MAO). Multiple blood samples were obtained for pharmacokinetic analyses of the two dosage forms on Days 1, 7, 8 and 14. Subjects were confined throughout the study (approximately 16 days) and remained in the clinic from approximately 36 hours prior to the first dose of the study drug (Day -2) until 24 hours after the administration of the last dose of lansoprazole.

Clinical Supplies: Lansoprazole 30 mg was dosed as a racemic mixture, theoretically consisting of 15 mg of the *R*(+)- enantiomer and 15 mg of the *S*(-)- enantiomer. The 30 mg lansoprazole capsules and 30 mg lansoprazole for intravenous infusion were manufactured by [redacted] and packaged and sent to the clinical research site by [redacted] on behalf of TAP Pharmaceutical Products Inc. Clinical supplies were stored at the investigational site in an appropriate, secure place.

Sample Collection: Five (5) mL blood samples were obtained from an indwelling catheter or by direct venipuncture for all subjects on Study Days 1 and 7 in Period 1 and Study Days 8 and 14 in Period 2 to determine the pharmacokinetic parameters of *R*(+)-, *S*(-) and total lansoprazole. Samples were collected into appropriately labeled heparinized tubes. For Period 1 (oral administration), blood samples were collected at the

following times: 0 hour (predose), 0.5, 1.0, 1.5, 2.0, 3.5, 6.0, 9.0, and 12 hours post dose. For Period 2 (intravenous infusion), blood samples were collected at 0 hour (predose), 10, 15, 20 and 30 minutes after the start of the infusion, and 0.25, 0.5, 1.0, 1.5, 2.0, 3.5, 6.0, 9.0, and 12 hours after the end of infusion.

Analytical Methodology: Plasma concentrations of *R*(+)- and *S*(-)- lansoprazole were determined at [] using a validated [] assay. The lower limit of quantitation (LLOQ) was [] ng/mL for both enantiomers using a plasma sample volume of 0.25 mL. Plasma samples were extracted and analyzed between March 18, 2002 and April 5, 2002. Plasma QC samples analyzed with each analytical run had coefficients of variation and absolute deviation values from nominal concentrations of $\leq 6.91\%$ and $\leq 4.20\%$ for *R*(+)-lansoprazole and $\leq 8.42\%$ and $\leq 2.40\%$ for *S*(-)-lansoprazole. The total lansoprazole plasma concentration was calculated as the sum of the measured *R*(+)- and *S*(-)-lansoprazole plasma concentrations.

Pharmacokinetic, and Statistical Analyses: The pharmacokinetic parameters of *R*(+)-, *S*(-)-, and total lansoprazole (calculated using the sum of the measured *R*(+)- and *S*(-)-lansoprazole plasma concentrations) on Days 1, 7, 8 and 14 were calculated using standard noncompartmental methods. These included: the maximum observed plasma concentration (C_{max}), the time to reach the maximum plasma concentration (T_{max}), the area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_0), the area under the plasma concentration-time curve from time zero to 24 hours (AUC_{24}), the area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}), the terminal elimination rate constant (λ_z) and the terminal elimination half-life ($t_{1/2}$). In addition, clearance (CL) and volume of distribution at steady-state (V_{ss}) were calculated for *R*(+), *S*(-) and total lansoprazole following the 30 mg intravenous dose of lansoprazole administered as a 30-minute infusion (Days 8 and

14). The individual plasma concentrations and pharmacokinetic parameters of lansoprazole were tabulated with descriptive statistics for Days 1 and 7 in Period 1 (oral) and for Days 8 and 14 in Period 2 (intravenous).

For pharmacokinetic analyses, the Day 8 dose was considered a single intravenous dose since all predose concentrations on Day 8 were below the lower limit of quantitation (LLOQ). The difference between a pharmacokinetic parameter for lansoprazole obtained following oral (Day 1 or 7) and intravenous (Day 8 or 14) doses was analyzed by a paired t-test for both the single dose (Days 1 and 8) and multiple doses (Days 7 and 14) at steady state. The pharmacokinetic parameters that were analyzed included T_{max} , λ_z , and the natural logarithmic transformed C_{max} and AUC's. The absolute bioavailability of lansoprazole after a single dose and multiple doses was calculated based on the point estimate for the ratios of central values following oral administration (Day 1 or 7) versus intravenous administration (Day 8 or 14) for C_{max} and $AUC_{0-\infty}$, respectively. A 95% confidence interval for each ratio was constructed by exponentiating the confidence limits for the difference of logarithm means obtained from the paired t-test analysis. Point estimates and 95% confidence intervals for the ratios of central values of C_{max} and AUC's were constructed to compare multiple doses (Day 14 or Day 7) vs. single dose (Day 8 or Day 1) of lansoprazole. For each day, point estimate and 95% confidence interval for the ratio of $R(+)$ - to total lansoprazole were derived as well.

Pharmacokinetic Results: Mean plasma pharmacokinetic parameters for $R(+)$ -, $S(-)$ -, and total lansoprazole after the administration of single and multiple 30 mg oral doses of lansoprazole on Days 1 and 7 are presented in the following table.

Appears This Way
On Original

Best Possible Copy

Mean Plasma Pharmacokinetic Parameters for R(+)-, S(-), and Total Lansoprazole on Days 1 and 7 Following Oral Administration of 30 mg Lansoprazole in Study M01-307

Compound	Study Day		T _{max} ^a (h)	C _{max} ^a (ng/mL)	AUC ₀₋₂₄ ^b (ng·h/mL)	AUC ₀₋₂₄ ^c (ng·h/mL)	t _{1/2z} ^b (h)
R(+)-Lansoprazole	1	Mean	1.66	712.99	1911.29	2223.79	1.12
		SD	0.65	264.17	1248.95	1473.13	
	7	Mean	1.75	701.90	1925.83	2407.41	1.17
		SD	0.73	312.11	1385.95	1525.31	
S(-)-Lansoprazole	1	Mean	1.52	102.88	149.11	ND	ND
		SD	0.70	100.30	190.63	ND	
	7	Mean	1.57	108.66	152.93	ND	ND
		SD	0.78	110.83	211.12	ND	
Total Lansoprazole	1	Mean	1.66	811.05	2078.34	2421.87	1.10
		SD	0.65	349.13	1435.88	1679.66	
	7	Mean	1.65	806.92	2099.46	2632.11	1.15
		SD	0.75	406.17	1597.89	1809.83	

a: N = 28. b: N = 20.
 c: Harmonic Mean.
 ND = Not Determined
 SD = Standard Deviation

The absorption of orally administered 30 mg lansoprazole was rapid, with mean T_{max} values of 1.5 to 1.8 hours for R(+)-, S(-)-, and total lansoprazole. After T_{max}, plasma concentrations of R(+)-, S(-)-, and total lansoprazole declined rapidly, with harmonic mean values for the terminal elimination half-life (t_{1/2z}) of R(+)- and total lansoprazole of approximately 1 hour. The terminal elimination half-life (t_{1/2z}) and AUC₂₄ could not be estimated for S(-)-lansoprazole because of a limited number of measurable concentrations in the terminal portion of the concentration versus time curves. Mean pharmacokinetic parameters for R(+)-, S(-)-, and total lansoprazole after oral administration of 30 mg lansoprazole for 7 days were generally similar to those observed after a single dose.

Mean plasma pharmacokinetic parameters for R(+)-, S(-)-, and total lansoprazole after single and multiple 30 mg intravenous doses of lansoprazole as a 30-minute infusion on Days 8 and 14 are presented in the following table.

Appears This Way
 On Original

Mean Plasma Pharmacokinetic Parameters for R(+), S(-), and Total Lansoprazole on Days 8 and 14 Following the Administration of 30 mg Intravenous Doses of Lansoprazole as a 30-Minute Infusion in Study M01-307

Compound	Study Day		T _{max} ^a (h)	C _{max} ^a (ng/mL)	AUC ₀₋₂₄ ^a (ng·h/mL)	AUC ₀₋₈ ^b (ng·h/mL)	CL ^b (L/h)	V _{ss} ^b (L)	t _{1/2z} ^c (h)
R(+)-Lansoprazole	8	Mean	0.51	1191.85	2353.96	2651.37	6.80	10.59	1.17
		SD	0.05	184.23	1300.31	1507.08	2.50	1.21	
	14	Mean	0.51	1175.53	2499.64	2825.10	6.62	10.59	1.21
		SD	0.05	184.21	1510.84	1826.59	2.65	1.34	
S(-)-Lansoprazole	8	Mean	0.48	518.34	493.74	540.47	31.08	21.10	0.56
		SD	0.06	117.53	219.06	241.55	8.26	3.81	
	14	Mean	0.48	480.60	489.08	540.39	31.53	22.67	0.59
		SD	0.06	116.78	232.55	260.58	9.13	3.50	
Total Lansoprazole	8	Mean	0.51	1705.31	2859.34	3191.84	11.12	15.66	1.13
		SD	0.05	291.91	1517.29	1744.75	3.84	1.90	
	14	Mean	0.50	1652.18	3001.82	3365.27	10.89	15.87	1.17
		SD	0.00	293.55	1741.84	2083.03	4.09	1.94	

a: N = 28, n: N = 20
 c: Harmonic Mean
 ND = Not Determined
 SD = Standard Deviation

The maximum plasma concentrations of R(+)-, S(-)-, and total lansoprazole were attained at the end of the 30-minute infusion. Thereafter, plasma concentrations of R(+)-, S(-)-, and total lansoprazole declined rapidly, with harmonic means for the terminal half-life (t_{1/2z}) ranging from 0.6 to 1.2 hours. The average terminal half-life of S(-)-lansoprazole was approximately 50% shorter than that of R(+)-lansoprazole. The pharmacokinetics of total lansoprazole and its enantiomers after daily intravenous 30 mg lansoprazole doses for 7 days were similar to those observed after a single intravenous dose.

Results for the point estimates and the 95% confidence intervals for the ratios of central values of oral vs intravenous lansoprazole with respect to R(+)-, S(-)-, and total lansoprazole C_{max} and AUC₀₋₂₄ following single or multiple doses are summarized in the following table.

Appears This Way
 On Original

Best Possible Copy

Absolute Bioavailability of R(+)- and Total Lansoprazole Following Oral Administration of Single (Day 1 vs. Day 8) or Multiple (Day 7 vs. Day 14) 30 mg Lansoprazole in Study M01-307

Compound	Dose	Pharmacokinetic Parameter	Central Value		Ratio of Central Values	
			Oral	Intravenous	Point Estimate	95% Confidence Interval
R(+)-Lansoprazole	Single	C_{max} ^a AUC_{24} ^b	[]	0.559	0.479 – 0.653
	Multiple	C_{max} ^a AUC_{24} ^b			0.811	0.766 – 0.858
0.530					0.430 – 0.654	
Total Lansoprazole	Single	C_{max} ^a AUC_{24} ^b			0.832	0.770 – 0.898
					0.437	0.370 – 0.516
	Multiple	C_{max} ^a AUC_{24} ^b			0.717	0.668 – 0.770
			0.425	0.340 – 0.531		
		0.745	0.680 – 0.815			

a: N = 24; b: N = 20

Best Possible Copy

The absolute bioavailability (F) of total lansoprazole was 72% to 75% based on the point estimate for the ratios of central values of AUC_{24} following oral administration (Day 1 or 7) versus intravenous administration (Day 8 or 14). The bioavailability of R(+)-lansoprazole was slightly higher than that of total lansoprazole (81% to 83%).

The point estimates and 95% confidence intervals for C_{max} and AUC values further supported that the pharmacokinetic parameters of R(+)-, S(-)- and total lansoprazole were similar after single and multiple doses of 30 mg lansoprazole.

The results obtained in this study demonstrated that the plasma exposure of lansoprazole was mainly due to R(+)-lansoprazole following both oral and intravenous administration. The ratio of central C_{max} values for R(+)- to total lansoprazole was approximately 0.9 following oral administration and 0.7 following intravenous administration. R(+)-lansoprazole accounted for 93% of total lansoprazole central AUC_{24} values following single or multiple oral doses, and 82% to 83% following single or multiple intravenous doses. The terminal half-lives ($t_{1/2}$) of R(+)- and total lansoprazole following intravenous infusion and oral administration were similar.

Conclusions: As expected, a 30 mg dose of lansoprazole administered as a 30-minute

Approve This Way
 Dis Approve This Way
 On Original

intravenous infusion resulted in higher C_{max} and AUC values for *R*(+)-, *S*(-)-, and total lansoprazole compared to a 30 mg oral dose of lansoprazole. *R*(+)-lansoprazole accounted for 93% of total lansoprazole exposure following oral administration and 82 to 83% following intravenous administration, indicating the total exposure of lansoprazole is predominantly due to *R*(+)-lansoprazole. For both routes of administration, half-life values were similar for *R*(+)- and total lansoprazole, while the average half-life for *S*(-)-enantiomer was approximately 50% shorter than that of *R*(+)- or total lansoprazole following intravenous administration of 30 mg lansoprazole. The absolute bioavailability (*F*) of total lansoprazole was 72% to 75% based on the ratio of central values for $AUC_{0-\infty}$ following oral administration versus intravenous administration. The bioavailability of *R*(+)-lansoprazole was slightly higher than that of total lansoprazole (81% to 83%). The pharmacokinetics of *R*(+)-, *S*(-)-, and total lansoprazole after repeated daily oral or intravenous doses of lansoprazole were similar to those observed following a single dose.

Best Possible Copy

Appears This Way
On Original

Figure 2. Mean R(+)-Lansoprazole, S(-)-Lansoprazole and Total Lansoprazole Plasma Concentration - Time Profiles on Day 1 and Day 7 Following Oral Administration of 30 mg Lansoprazole

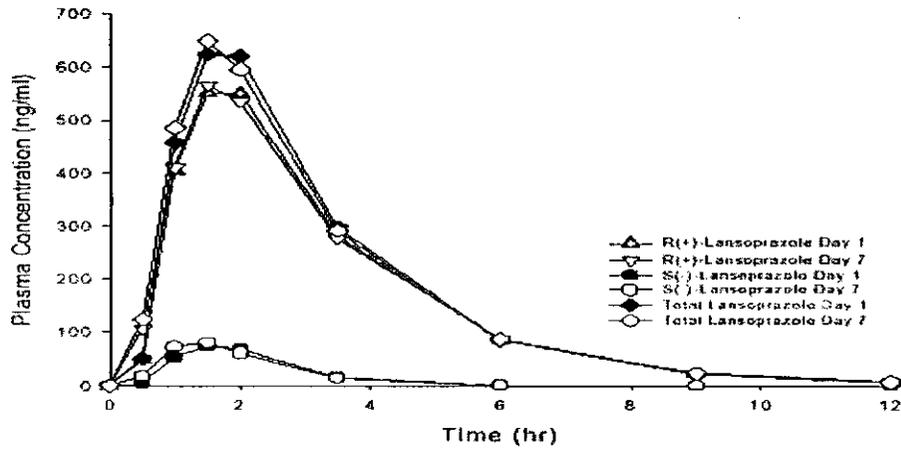
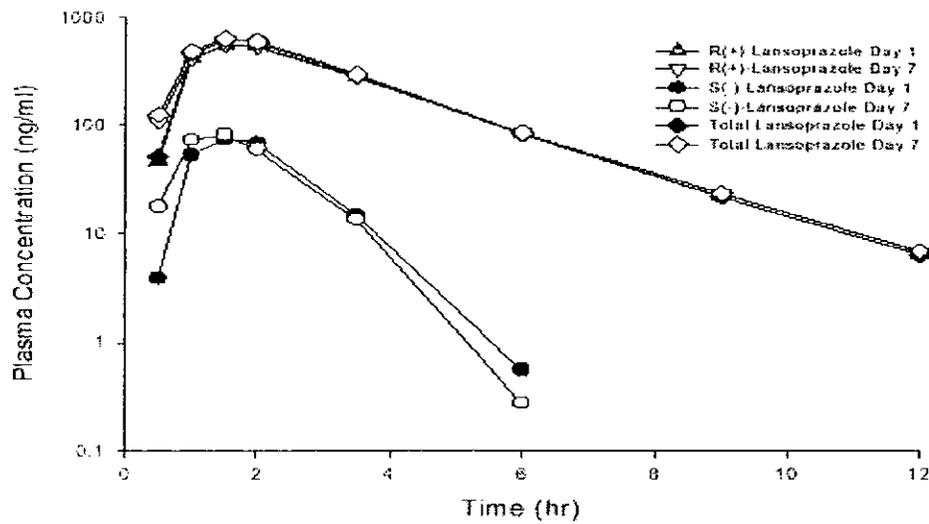


Figure 3. Mean R(+)-Lansoprazole, S(-)-Lansoprazole and Total Lansoprazole Plasma Concentration - Time Profiles on Day 1 and Day 7 Following Oral Administration of 30 mg Lansoprazole



Best Possible Copy

Figure 4. Mean R(+)-Lansoprazole, S(-)-Lansoprazole and Total Lansoprazole Plasma Concentration -Time Profiles on Day 8 and Day 14 Following Intravenous Infusion of 30 mg Lansoprazole

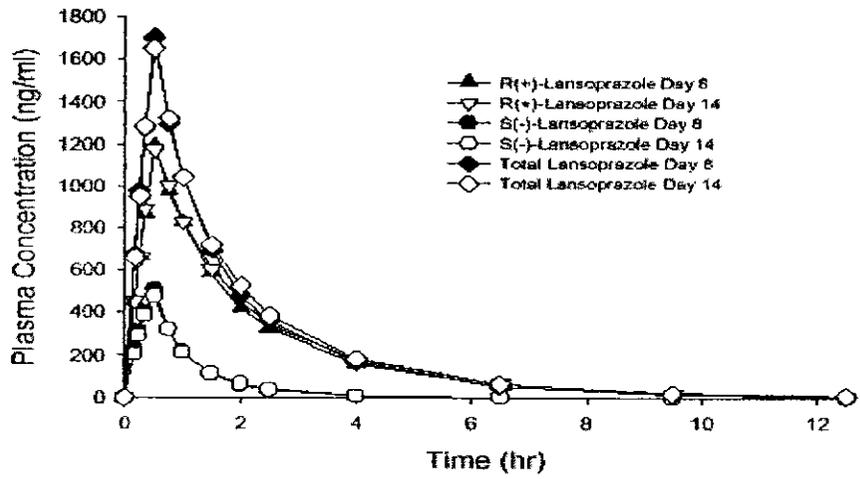
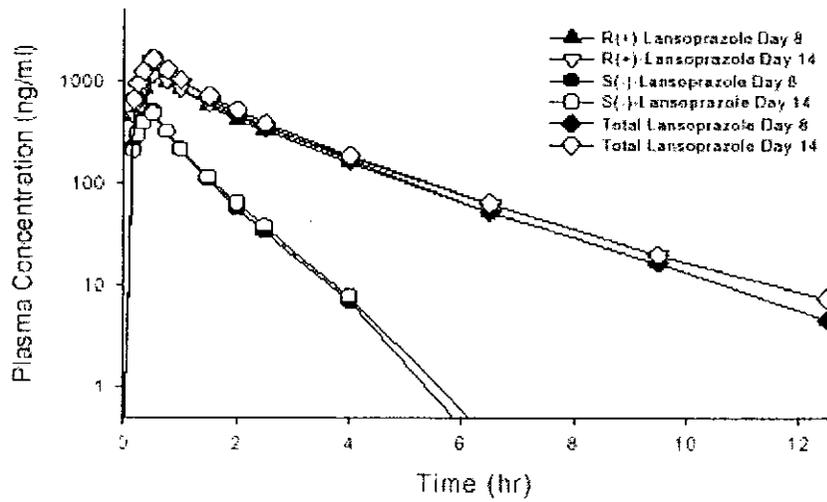


Figure 5. Mean R(+)-Lansoprazole, S(-)-Lansoprazole and Total Lansoprazole Plasma Concentration -Time Profiles on Day 8 and Day 14 Following Intravenous Infusion of 30 mg Lansoprazole



Study No. M95-306 (Vol. 1.21)

Summary

Title: A Randomized, Open-Label, Crossover, Single-Center Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Single Doses of Intravenous Lansoprazole (Abbott-65006, Prevacid®) in Healthy Subjects (Protocol M95-306)

Objective: The objective of this study was to determine the safety, pharmacokinetics and pharmacodynamics of single doses of IV lansoprazole compared to those of a 30 mg oral dose of lansoprazole. This report addresses the pharmacokinetic and some of the pharmacodynamic aspects of this study.

Investigator: []

]

Study Dates: April 29, 1996 through June 12, 1996.

Subjects: A total of thirty-eight (38) nonsmoking healthy male and female subjects were enrolled and thirty-three of these subjects completed the study. There were 31 male and 2 female subjects who completed the study. The mean age was 30.6 years (range: 19 to 45 years), the mean weight was 81.9 kilograms (range: 65.8 to 97.5 kg) and the mean height was 177.8 centimeters (range: 162.6 to 193.0 cm).

Drug Supplies: Study medication was supplied as oral lansoprazole capsules (30 mg [] per capsule) or intravenous lansoprazole (as a lyophilized powder containing 30 mg of lansoprazole in each vial), and diluent (5 mL ampules composed of 1500 mg polyethylene glycol 400, HCl and water). Each vial of IV lansoprazole was mixed with one ampule of diluent at time of dosing. All medications were supplied by [] and packaged by [] (as finishing Lot No. 15-432-S2, NPRO 8221) on the behalf of TAP Holdings Inc. Individual lot numbers were as follows:

Drug	Lot Nos.		
	NPRO	Finishing Lot	Manufacture
Lansoprazole capsules, 30 mg A-65006	6917N	06-184-AR-03	2523V111
Lansoprazole, vials, 30 mg lyophilized	7004N	12-168-AL	23387231
Diluent, 5 ml, ampules	7005N	12-167-AL	23385091

Appears This Way
On Original

Study Design and Dosing Regimen: This was a Phase I, randomized, open-label, six-way crossover study comparing single doses of IV lansoprazole to a 30 mg oral dose of lansoprazole. Subjects were randomly assigned in equal numbers to one of six sequences of regimens. The sequences were such that each subject participated in all six regimens, and in each period, regimens were assigned an equal number of subjects. Listed below are the six regimens:

- Regimen A: Lansoprazole 30 mg capsule PO
- Regimen B: Vehicle only IV, 10 mL (30 minute infusion)
- Regimen C: Lansoprazole 30 mg, 5 mL IV (120 minute infusion)
- Regimen D: Lansoprazole 30 mg, 5 mL IV (60 minute infusion)
- Regimen E: Lansoprazole 30 mg, 5 mL IV (30 minute infusion)
- Regimen F: Lansoprazole 60 mg, 10 mL IV (30 minute infusion)

Subjects were dosed in three groups of twelve. Group I consisted of Subjects 101-112, Group II consisted of Subjects 113-124. Subjects 115 and 116 discontinued after Period I and replaced by Subjects 137 and 138. Group III consisted of Subjects 125-136.

Blood Sampling: Five (5) mL blood samples were collected by venipuncture into appropriately labeled heparinized collection tubes and immediately placed in ice. Plasma from the blood samples was separated by centrifugation, transferred to appropriately labeled tubes (2 tubes/sample), and frozen at a maximum temperature of -19°C. A schematic detailing sampling time intervals with each regimen follows.

Dose	Length of Infusion	Relative to Start of the Infusion	Relative to End of the Infusion (Post-Dose for PO)
		Sample Collection Times	
30 mg PO	N/A	N/A	0, 0.5, 1, 1.5, 2, 3.5, 6, 9 & 12 hours
30, 60 mg IV & Vehicle Only	30 Minute	0 (pre), 10, 15, 20 and 30* minutes	0.25, 0.5, 1, 1.5, 2, 3.5, 6, 9 and 12 hours
30 mg IV	60 Minute	0 (pre), 10, 15, 20, 30, 45 & 60* minutes	0.25, 0.5, 1, 1.5, 2, 3.5, 6, 9 & 12 hours
30 mg IV	120 Minute	0 (pre), 10, 20, 30, 45, 60, 90 & 120* minutes	0.25, 0.5, 1, 1.5, 2, 3.5, 6, 9 & 12 hours

*Note: Samples obtained at 30, 60 and 120 minutes after the start of the 30, 60 and 120 minute infusions were collected prior to the infusions ending
 N/A = Not Applicable

Best Possible Copy

Appears This Way
 On Original

Analytical Methodology: Venous plasma samples were analyzed using a validated HPLC method for lansoprazole at []

Gastric pH Measurement: Gastric pH was measured on the day of dosing of each crossover period for 24-hours, beginning one hour prior to dose administration, using a []

Pharmacokinetic Analyses: For each lansoprazole regimen the following parameters were determined: maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), terminal elimination phase rate constant (β), the associated half-life ($t_{1/2}$), area under the concentration-time curve ($AUC_{0-\infty}$), calculated by the trapezoidal rule with extrapolation from the last measurable concentration, area under the first moment curve (AUMC), and clearance (CL). Also calculated for IV regimens were mean residence time (MRT) and steady state volume (V_{ss}).

Statistical Analyses: A p-value less than or equal to 0.05 was considered statistically significant.

An analysis of variance (ANOVA) was performed for T_{max} and β and the logarithms of C_{max} , and $AUC_{0-\infty}$ (with normalization of the 60 mg dose values to a 30 mg dose). The ANOVA had effects for group, subject nested within group, regimen, period, regimen-group interaction, and period-group interaction. Within the framework of the ANOVA each 30 mg infusion was compared to the 30 mg oral dose at a significance level of 0.05. The 30 minute infusions of 30 and 60 mg were also compared at a significance level of 0.05. Relative bioavailabilities were assessed within the context of the ANOVA model.

ANOVAs were also carried out for intragastric average pH over 23 hours and for percents of time that pH exceeded 3, 4, 5 and 6. The ANOVA had effects for group, sequence, group-sequence interaction, subject nested within group-sequence combination, regimen, period, regimen-group interaction, and period-group interaction. The effects of subject were random, and all other effects were fixed. Within the framework of the ANOVA,

Appears This Way
On Original

Best Possible Copy

each lansoprazole regimen was compared to the vehicle control, and each lansoprazole IV regimen was compared to the oral dose.

Results: A summary of the pharmacokinetic results for lansoprazole is presented in the following table:

Regimen	Mean Lansoprazole Parameters				
	Dose (mg) / IV infusion duration (min)				
	A 30 mg Oral	C 30/120	D 30/60	E 30/30	F 60/30
C_{max} (ng/mL)	681.8	934.4	1346.4	1736.4	3588.5
T_{max} (h)	2.0	2.0	1.0	0.5	0.5
$AUC_{0-\infty}$ (ng·h/mL)	2309.0	3012.3	3162.5	3103.3	7130.2
F^{\dagger}	0.67 - 0.72	-	-	-	-
$t_{1/2}$ (h) [‡]	1.2	1.1	1.1	1.1	1.2
MRT (h)		1.9	1.7	1.7	1.9
CL (L/h)	19.5 [§]	13.4	12.7	12.8	10.5
V_{ss} (L)		20.6	17.5	17.7	16.3

[†] Based on comparisons to regimens C, D, and E. Appendix B.

[‡] Presented as Harmonic Mean

[§] CL/F

There were statistically significant differences in T_{max} upon comparison of the 60 and 30 minute IV administration to the oral administration but not for the 120 minute IV administration as compared to the oral administration. C_{max} values for the 30 mg oral dose were statistically significantly different from the C_{max} values for 30-mg lansoprazole administered over 30, 60, or 120 minutes. Dose-normalized C_{max} values for 30-mg or 60-mg lansoprazole administered IV over 30 minutes were not statistically significantly different. Statistically significant differences were seen in β , implying differences in half-life; however, the differences were small and inconsequential. Dose-normalized AUC following administration of lansoprazole orally was statistically significantly different from each of the intravenous administrations.

All the lansoprazole regimens produced statistically significantly higher mean pH values than the vehicle control regimen. Analyses of intragastric pH determinations showed no statistically significant differences between the mean pH values over 23 hours for any of the 30 mg IV doses when compared to the 30 mg oral dose. There were no statistically significant differences between the 30 mg oral dose and the 30 mg IV doses used in this

Best Possible Copy

study with regard to the percent of time the pH was greater than 3, 4, 5 or 6, with the exception of the 30 mg IV dose over 60 minutes compared to 30 mg oral dose for pH >3 ($p=0.043$).

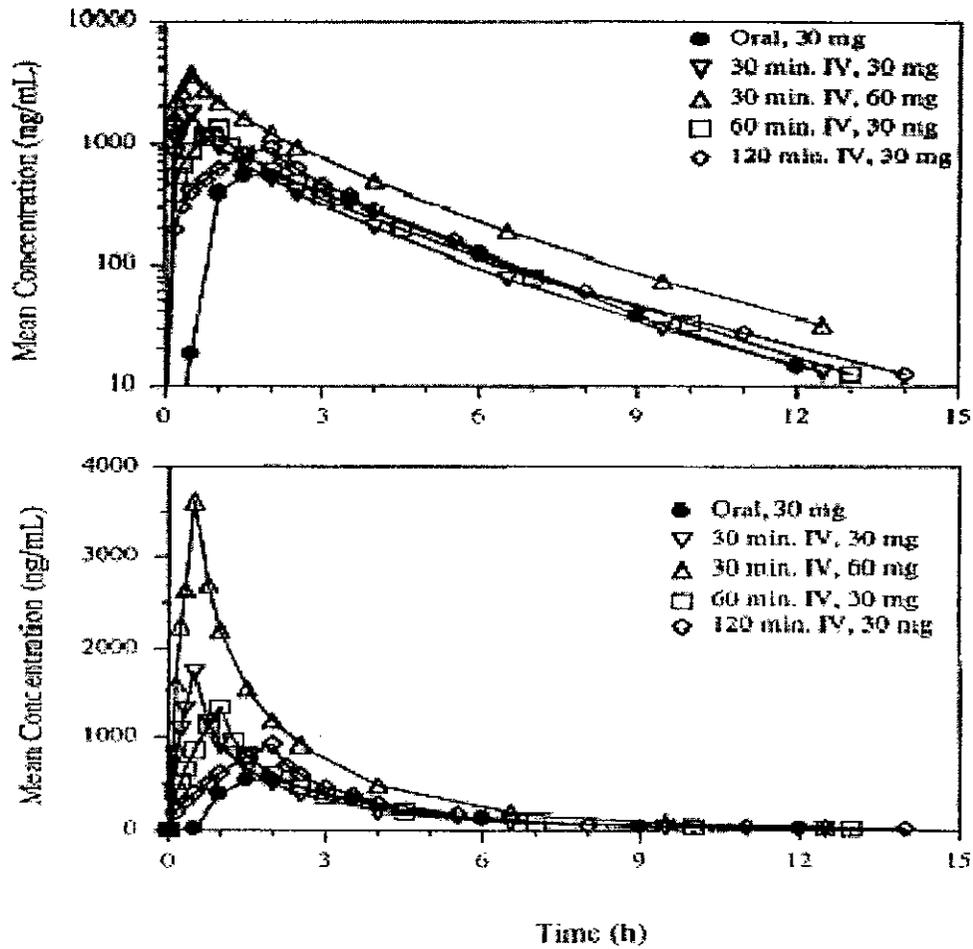
Conclusions: Differences observed between oral and intravenous values of T_{max} and C_{max} were as expected upon consideration of the intrinsic characteristics of these routes of administration. Half-lives were similar across doses and routes. Absolute bioavailabilities ranged from 0.64 to 0.74, depending upon intravenous reference. 95% confidence intervals ranged from 0.61 to 0.78 depending upon reference. Based on mean pH over a 23 hour period and time above various target pH levels, acid suppression following administration of 30 mg IV was at least as good and generally not significantly different from the oral 30 mg dose.

Table 1.

	Summary of pH Assessments			
	Regimen			
	30 mg PO	30 mg over 120 min	30 mg over 60 min	30 mg over 30 min
Mean pH, 0-23 h	3.16	3.44	3.59	3.39
Percent of time pH >				
3	43.46	51.75	54.64	59.34
4	32.85	39.39	41.29	36.77
5	18.24	23.43	23.84	19.31
6	10.58	13.67	13.02	11.34

Appears This Way
On Original

Figure 1. Mean Lansoprazole Plasma Concentration Time Profiles after Oral and IV Administrations



Study No. M96-486 (Vol. 1.22)

Summary

Title: A Randomized, Open-Label, Crossover, Single-Center Study to Evaluate the Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Doses of Intravenous Lansoprazole in Healthy Subjects (Protocol M96-486)

Objective: The objective of this study was to determine the tolerability, pharmacokinetics and pharmacodynamics of lansoprazole 30 mg (intravenously) compared to those of lansoprazole 30 mg (orally) when administered for 5 consecutive days. This report addresses the pharmacokinetics of lansoprazole and the overall outcome of the 24-hour intragastric pH measurements.

Investigator and Study Dates: This study was conducted at [] The principal investigator was [] Dosing of the subjects occurred between October 9, 1999 and March 17, 2000

Subjects: A total of 36 healthy adult subjects (24 males and 12 females) participated in the study, where 34 subjects completing all four periods, and two subjects completing at least one period of the study. Of these 36 subjects, 31 were Hispanic, four were Caucasian and one was of mixed race. The 36 subjects had mean \pm SD (min - max) age, body weight and height of 34.3 ± 6.3 (20 - 42) years, 73.3 ± 9.8 (53.1 - 94.3) kg and 168.7 ± 9.4 (149.9 - 188) cm, respectively.

Study Design and Dose Administration: This was a Phase I, randomized, open-label, four-way crossover, single-center study to compare 5-day, once daily administration of a 30 mg intravenous (IV) dose of lansoprazole with and without polyethylene glycol 400 (PEG) diluent to an intravenous injection of the vehicle with PEG for lansoprazole and to a 30 mg oral dose of lansoprazole. In Regimen A, one 30 mg lansoprazole capsule was administered with 180 mL of water. In Regimen B, 5 mL of PEG diluent (vehicle) was administered as an intravenous infusion in 50 mL of 0.9% NaCl over 30 minutes. In Regimen C, 30 mg of lansoprazole mixed in 5 mL of PEG diluent was administered as an intravenous infusion in 50 mL of 0.9% NaCl over 30 minutes. In Regimen D, 30 mg of lansoprazole mixed in 5 mL of 0.9% NaCl was administered as an intravenous infusion in 50 mL of 0.9% NaCl over 30 minutes. Each dose was administered once

Best Possible Copy

Appears This Way
On Original

Pharmacokinetic Parameter	(-) Lansoprazole ^d					
	Regimen A (N=34)		Regimen C (N=35)		Regimen D (N=36)	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
C _{max} (ng/mL)	577.8 ± 368.6	909.8 ± 297.7	1318 ± 290.1	1334 ± 257.6	1298 ± 216.7	1369 ± 313.8
T _{max} (h)	1.7 ± 0.8	1.6 ± 0.6	0.5 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
AUC ₀₋₂₄ (ng·h/mL)	2627 ± 1456	2843 ± 1704	3055 ± 1442	3150 ± 1603	2897 ± 1335	3049 ± 1447
F ^e	0.81, 0.83	0.84, 0.85	—	—	—	—
t _{1/2} ^f (h)	1.26 ± 0.39 ^g	1.23 ± 0.39 ^h	1.24 ± 0.36	1.26 ± 0.40	1.20 ± 0.35	1.23 ± 0.36
MRT (h)	—	—	2.0 ± 0.8	2.0 ± 1.0	1.9 ± 0.8	1.9 ± 0.9
CL (L/h)	7.0 ± 4.1 ⁱ	6.9 ± 4.0 ^h	5.9 ± 2.5	5.8 ± 2.5	6.1 ± 2.5	5.8 ± 2.4
V _{ss} (L)	—	—	10.4 ± 2.4	10.4 ± 2.2	10.4 ± 1.9	10.3 ± 2.0

Pharmacokinetic Parameter	(-) Lansoprazole ^d					
	Regimen A (N=34)		Regimen C (N=35)		Regimen D (N=36)	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
C _{max} (ng/mL)	151.5 ± 122.8	152.9 ± 95.7 ^h	536.3 ± 169.3	522.1 ± 128.7	536.6 ± 141.7	524.8 ± 145.7
T _{max} (h)	1.6 ± 0.7	1.4 ± 0.5 ^h	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
AUC ₀₋₂₄ (ng·h/mL)	250.5 ± 218.9	267.0 ± 121.9 ^h	591.1 ± 219.6	576.7 ± 214.5	568.0 ± 203.4	562.7 ± 201.1
F ^e	0.28, 0.29	0.31, 0.31	—	—	—	—
t _{1/2} ^f (h)	0.66 ± 0.17 ^g	0.52 ± 0.18 ^d	0.68 ± 0.17	0.67 ± 0.18	0.62 ± 0.14	0.63 ± 0.17
MRT (h)	—	—	0.9 ± 0.3	0.9 ± 0.3	0.8 ± 0.3	0.8 ± 0.3
CL (L/h)	76.7 ± 63.1 ⁱ	77.3 ± 53.1 ^h	28.3 ± 9.2	29.1 ± 9.0	29.0 ± 8.7	29.6 ± 9.3
V _{ss} (L)	—	—	27.8 ± 6.8	28.5 ± 7.2	27.3 ± 9.8	27.7 ± 8.0

Pharmacokinetic Parameter	Total Lansoprazole ^d					
	Regimen A (N=34)		Regimen C (N=35)		Regimen D (N=36)	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
C _{max} (ng/mL)	1027 ± 474.5	1052 ± 385.6	1453 ± 416.0	1449 ± 376.0	1414 ± 354.0	1460 ± 424.5
T _{max} (h)	1.7 ± 0.8	1.5 ± 0.6	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
AUC ₀₋₂₄ (ng·h/mL)	2876 ± 1660	3101 ± 1919	3647 ± 1654	3726 ± 1827	3463 ± 1425	3611 ± 1637
F ^e	0.73, 0.75	0.76, 0.77	—	—	—	—
t _{1/2} ^f (h)	1.24 ± 0.38 ^g	1.20 ± 0.39 ^h	1.20 ± 0.37	1.21 ± 0.42	1.15 ± 0.36	1.19 ± 0.37
MRT (h)	—	—	1.3 ± 0.7	1.8 ± 0.9	1.7 ± 0.7	1.7 ± 0.8
CL (L/h)	15.0 ± 8.2 ⁱ	12.9 ± 7.9 ^h	9.7 ± 3.9	9.7 ± 3.9	10.2 ± 3.9	9.7 ± 3.8
V _{ss} (L)	—	—	16.7 ± 3.4	16.7 ± 3.1	16.7 ± 2.5	16.6 ± 2.9

^d Regimen A: Lansoprazole 30 mg QD × 5 days (Oral)
 Regimen C: Lansoprazole 30 mg with PEG QD × 5 days (No minute IV infusion)
 Regimen D: Lansoprazole 30 mg with 0.9% NaCl QD × 5 days (30 minute IV infusion)
^e Absolute bioavailability based on peak estimates, with Regimen C as 100% reference.
^f Harmonic mean ± pseudo-standard deviation.
^g Evaluation of t_{1/2} were based on statistical tests for β.
^h CL_{1/2}.
ⁱ N=31, n=3; N=33, n=3; N=30, n=3.

Appears This Way
On Original

On Day 1 and Day 5, the central values for total lansoprazole C_{max} and AUC_{24} with oral administration (Regimen A) were 50 – 53% and 73 – 77%, respectively, of those with intravenous infusion administrations (Regimens C and D). The fraction of (+) vs total lansoprazole in plasma following oral administration was 93% on both Day 1 and Day 5, and was 83 and 84% on Day 1 and Day 5, respectively, following either intravenous administrations. The two one-sided tests procedure based on analyses of the log-transformed (+), (-), and total lansoprazole C_{max} and AUC_{24} showed that the two intravenous regimens were bioequivalent. The pharmacokinetics of (+), (-), and total lansoprazole did not change with time after 5-day once daily repeated oral or intravenous administration of 30 mg lansoprazole.

A summary of the mean intragastric pH values and the mean percentages of time that the intragastric pH values remained above 3, 4, 5 and 6 during the entire 24-hour monitoring period on Days 1 and 5 is presented in the following table.

Lansoprazole Pharmacodynamics	Baseline	Regimen ¹			
		A	B	C	D
Day 1					
N	35	33	35	35	35
Mean 24-hour pH	3.33	4.75 [†]	3.45 [†]	4.95 [†]	4.86 [†]
% of time pH > 3	45.22	74.08 [†]	46.90 [†]	79.12 [†]	78.36 [†]
% of time pH > 4	31.07	67.18 [†]	36.54 [†]	71.83 [†]	70.51 [†]
% of time pH > 5	17.62	51.28 [†]	22.91 [†]	55.00 [†]	53.34 [†]
% of time pH > 6	11.90	29.96 [†]	14.80 [†]	31.82 [†]	28.98 [†]
Day 5					
N	35	34	35	35	35
Mean 24-hour pH	3.33	5.25 [†]	3.28 [†]	5.27 [†]	5.36 [†]
% of time pH > 3	45.22	83.92 [†]	44.05 [†]	85.57 [†]	85.54 [†]
% of time pH > 4	31.07	77.01 [†]	30.97 [†]	79.40 [†]	79.86 [†]
% of time pH > 5	17.62	63.59 [†]	18.54 [†]	63.78 [†]	64.92 [†]
% of time pH > 6	11.90	49.20 [†]	11.39 [†]	57.54 [†]	41.61 [†]

- † Regimen A: Lansoprazole 30 mg QD × 5 days (Oral)
 † Regimen B: Vehicle with PEG QD × 5 days (30 minute IV infusion)
 † Regimen C: Lansoprazole 30 mg with PEG QD × 5 days (30 minute IV infusion)
 † Regimen D: Lansoprazole 30 mg with H₂O₂ Sol. QD × 5 days (30 minute IV infusion)
 † Statistically significantly different (p < 0.05) from Regimen A
 † Statistically significantly different (p < 0.05) from Regimen B

On both Day 1 and Day 5 the mean 24-hour intragastric pH measurements obtained

Best Possible Copy

Appears This Way
On Original

after administration of Regimens A, C, and D were similar and were all statistically significantly higher than those of the intravenous vehicle administration (Regimen B). Also, Regimens A, C, and D maintained the intragastric pH values above 3, 4, 5, and 6 for relatively similar periods of time that were significantly longer than those with Regimen B. Compared to Day 1, the Day 5 mean 24-hour intragastric pH values were elevated to higher levels and were maintained above several threshold levels for longer periods of time with the administration of Regimens A, C, and D. On both Day 1 and Day 5, the two one-sided tests procedure based on analyses of mean 24-hour intragastric pH showed that Regimens C and D were pharmacologically equivalent to Regimen A. Also, Regimens C and D were pharmacologically equivalent on both Day 1 and Day 5.

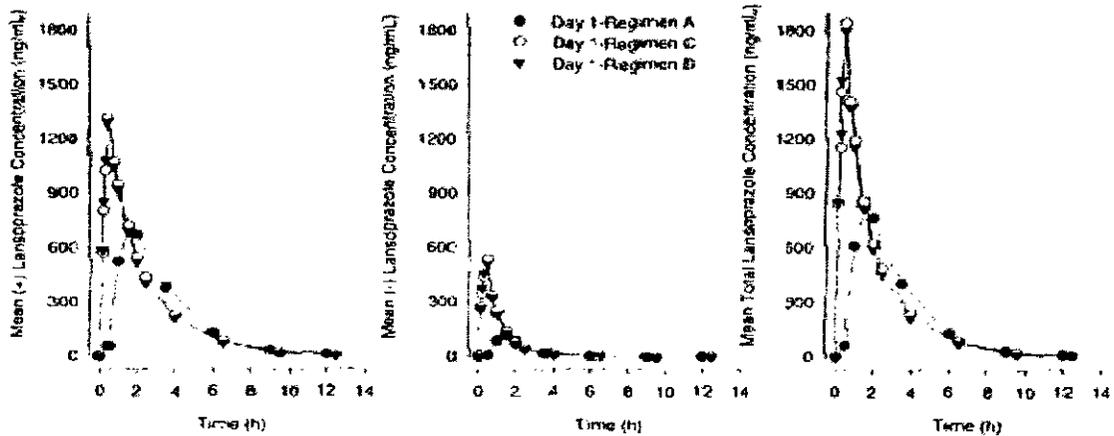
Conclusions: On both Day 1 and Day 5, 30-minute intravenous infusion of 30 mg lansoprazole with or without polyethylene glycol diluent leads to higher C_{max} and AUC_{24} values for (+), (-), and total lansoprazole compared to oral administration of 30 mg lansoprazole. Small differences between oral and intravenous regimens in the relative ratios of plasma (+) or (-) lansoprazole vs. total lansoprazole exist, but are not expected to have any clinical significance. Even though the (+), (-), and total lansoprazole pharmacokinetic profiles are lower after oral compared to intravenous administration, the intravenously administered 30 mg lansoprazole (with or without polyethylene glycol diluent) is pharmacologically equivalent to the orally administered 30 mg lansoprazole on both Day 1 and Day 5.

After 5-day once daily repeated oral or intravenous administration of 30 mg lansoprazole, the pharmacokinetics of (+), (-), and total lansoprazole do not change with time, but the pharmacodynamics of lansoprazole are enhanced. Compared to Day 1, the Day 5 mean 24-hour intragastric pH values are elevated to higher levels and are maintained above several threshold levels for longer periods of time.

Because intravenous administration of 30 mg lansoprazole with or without polyethylene glycol diluent yields equivalent pharmacokinetic and pharmacodynamic profiles of lansoprazole, it is evident that the 0.9% normal saline can be used as a diluent for lansoprazole intravenous administration in a clinical setting.

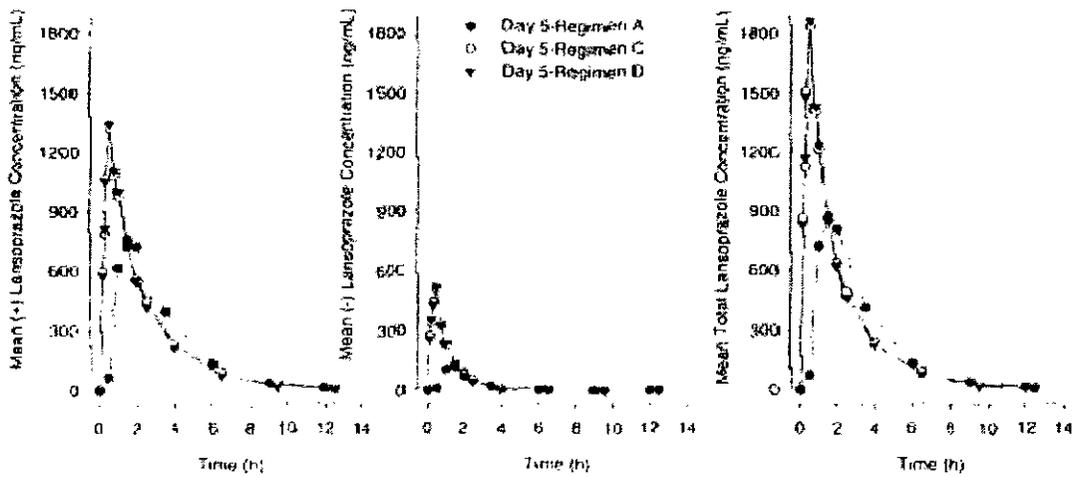
Appears This Way
On Original

Figure 1. Mean Lansoprazole Plasma Concentration - Time Profiles on Day 1



Regimen A: Lansoprazole 30 mg QD x 5 days (Oral)
 Regimen C: Lansoprazole 30 mg with TEG QD x 5 days (Intravenous)
 Regimen B: Lansoprazole 30 mg with 0.9% NaCl QD x 5 days (Intravenous)

Figure 2. Mean Lansoprazole Plasma Concentration - Time Profiles on Day 5



Regimen A: Lansoprazole 30 mg QD x 5 days (Oral)
 Regimen C: Lansoprazole 30 mg with TEG QD x 5 days (Intravenous)
 Regimen D: Lansoprazole 30 mg with 0.9% NaCl QD x 5 days (Intravenous)

Best Possible Copy

Figure 3. Mean Lansoprazole Plasma Concentration - Time Profiles for Regimen A (Oral Administration of Lansoprazole 30 mg QD)

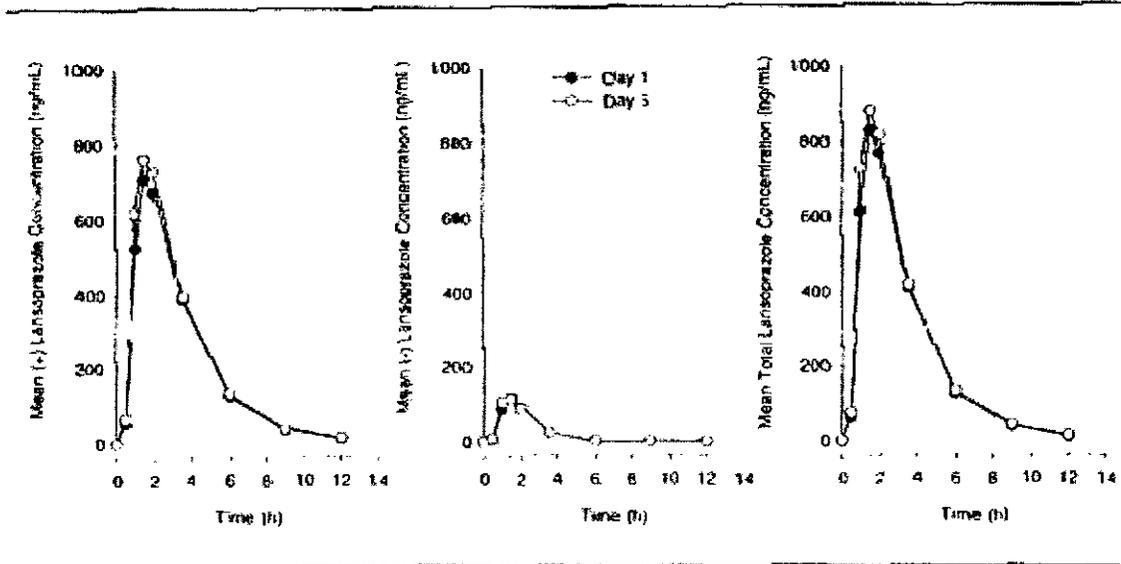


Figure 4. Mean Lansoprazole Plasma Concentration - Time Profiles for Regimen C (30 Minute Intravenous Infusion of Lansoprazole 30 mg QD with PEG)

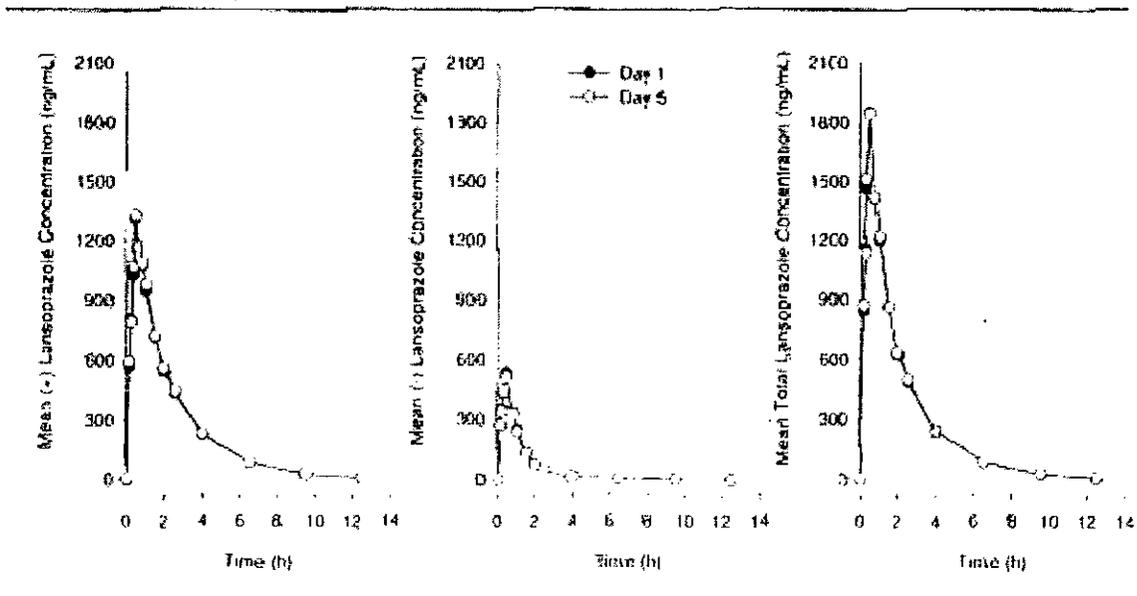


Figure 5. Mean Lansoprazole Plasma Concentration - Time Profiles for Regimen D (30 Minute Intravenous Infusion of Lansoprazole 30 mg QD with 0.9% NaCl)

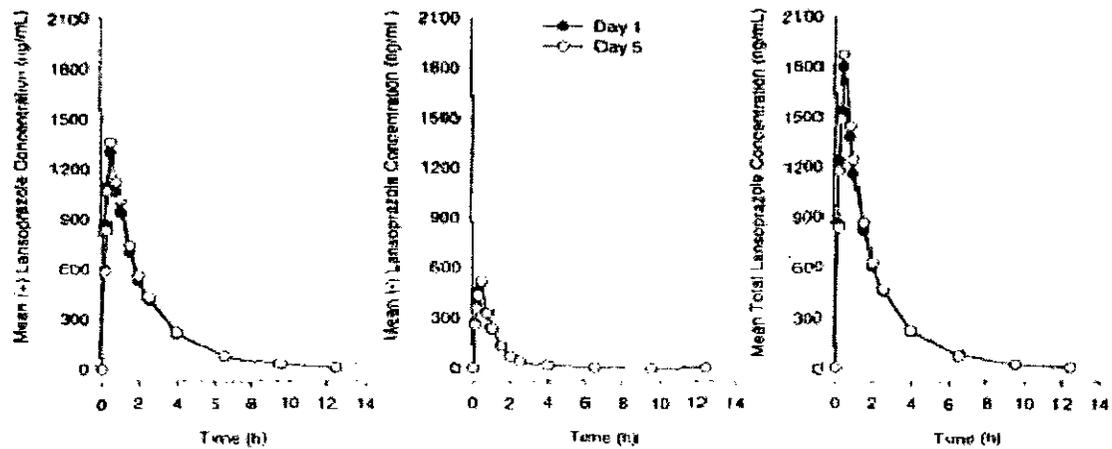


Figure 6. Mean Intra-gastric pH - Time Profiles for Baseline and with the Administrations of Regimens A - D on Day 1

- Baseline
- ▲ Regimen A - 30 mg Lansoprazole QD x 5 days (Oral)
- Regimen B - Vehicle with PEG QD x 5 days (IV)
- ◆ Regimen C - 30 mg Lansoprazole with PEG QD x 5 days (IV)
- ▼ Regimen D - 30 mg Lansoprazole with 0.9% NaCl QD x 5 days (IV)

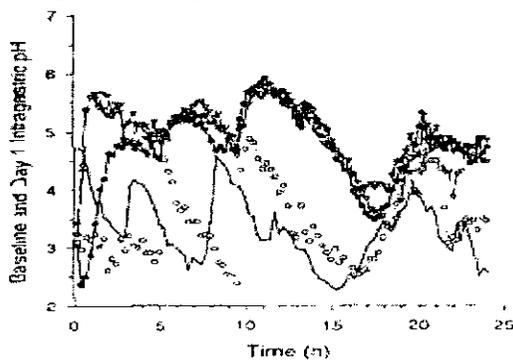
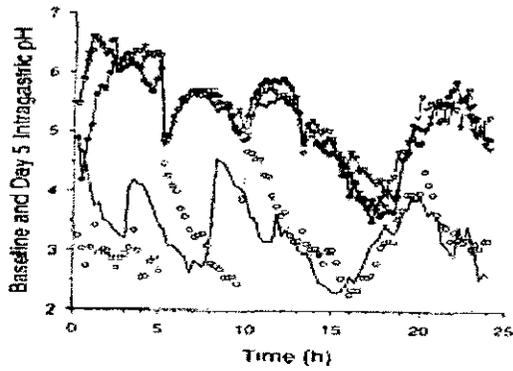


Figure 7. Mean Intra-gastric pH - Time Profiles for Baseline and with the Administrations of Regimens A - D on Day 5

- Baseline
- Regimen A - 30 mg Lansoprazole QD x 5 days (Oral)
- Regimen B - Vehicle with PEG QD x 5 days (IV)
- Regimen C - 30 mg Lansoprazole with PEG QD x 5 days (IV)
- Regimen D - 30 mg Lansoprazole with 0.9% NaCl QD x 5 days (IV)



Appears This Way
On Original

Study M01-308 (Vol. 1.23)

Lansoprazole (006)
 Study No. M01-308
 Clinical/Statistical Report
 Incorporating Administrative Change No. 1
 TAP-02-000091-2.0

Page 9

2.0 SYNOPSIS

Name of Company: TAP Pharmaceutical Products Inc.		Individual Study Table Referring to Item of the Submission: N/A Volume: N/A Pages: N/A
Name of Finished Product: Prevacid®		
Name of the Active Ingredient: Lansoprazole		
Title of Study: A Randomized, Placebo-Controlled, Multi-Center Study to Evaluate the Pharmacodynamics of Intravenous Lansoprazole to that of Oral Lansoprazole in Subjects with Erosive Esophagitis		
Investigator(s): 13 investigator sites (a list of all participating investigators is included in Appendix 16.1.4).		
Study Centers: Multicenter United States		
Publication (reference): None		
Study Period: 9 months Study Initiation Date: 22 Jan 2002 Study Completion Date: 23 May 2002		Phase of Development: 2
Objective: The objective of this study was to compare the pharmacodynamics of intravenous (IV) lansoprazole 30 mg to oral (PO) lansoprazole 30 mg (capsules) in subjects with erosive esophagitis.		
Methodology: This was a two-period study to evaluate the pharmacodynamics of IV lansoprazole 30 mg and oral lansoprazole 30 mg (capsules) in subjects with erosive esophagitis confirmed by endoscopy. Each subject completed all screening procedures in the 2 weeks immediately prior to beginning study drug. Screening procedures included a complete medical history, physical examination, including 12-lead electrocardiogram (ECG), routine ophthalmic examination (visual acuity and fundoscopic examination), laboratory evaluations, and endoscopy. Diaries were dispensed to each subject to be completed daily. Subjects who successfully completed the screening procedures were eligible to enter the study. During the treatment period, subjects received open-label lansoprazole 30 mg orally once daily for seven consecutive days (Period 1) and then received IV lansoprazole 30 mg or IV placebo (without a washout period) for the following seven consecutive days (Period 2) in a double-blind fashion. Subjects were randomized to active IV lansoprazole 30 mg versus IV placebo in a three to one ratio. Celestix® was provided for symptom relief throughout the entire study. During Period 1 (Study Days 1-6), oral drug was self-administered each morning approximately 30 minutes prior to the first meal or snack. On the morning of Study Day 7, subjects took the last dose of oral study drug in the clinic prior to the first meal or snack at approximately 1100. Likewise, during Period 2 (Study Days 8-14), active drug or placebo was administered intravenously at approximately 1100 hours. On three occasions during the study, gastric contents were collected (24 hours after the last dose of study drug) for 1 hour to determine basal acid output (BAO) and then collected for 2 hours to determine maximal acid output (MAO). These three occasions were: prior to dosing on Study Day 8 (evaluating the last dose of oral administration), prior to dosing on Study Day 9 (evaluating the first dose of IV administration), and on the morning of Study Day 15 (evaluating the last dose of IV administration). During the treatment period, subjects were asked to complete a daily diary to document the frequency of Celestix® use and the exact time of self-administration of oral study medication.		

Best Possible Copy

Methodology (continued):			
The safety of study drug was monitored through adverse events, concurrent medication utilization, vital signs, physical examinations, routine ophthalmic examination (visual acuity and funduscopic examinations), laboratory evaluations, 12-lead ECG, and IV infusion site assessments.			
At the completion of the study, the physician may have chosen to prescribe an 8-week oral course of Prevacid® 30 mg to heal the subject's erosive esophagitis. The expense for this medication was covered by the sponsor.			
No. of Subjects (Planned and Analyzed):			
	Oral lansoprazole 30 mg / IV Placebo	Oral lansoprazole 30 mg / IV lansoprazole 30 mg	
Number of Subjects Planned	18	54	
Number of Subjects Analyzed	20	67	
Diagnosis and Main Criteria for Inclusion:			
Volunteer subjects were male or female at least 18 years of age and had endoscopically documented erosive esophagitis.			
Test Product, Dose and Mode of Administration, Lot Number:			
Test Product	Dose	Mode of Administration	Finishing Sublot Number
Lansoprazole for injection	30 mg	intravenous	Z3387273, Z3387274
Reference Therapy, Dose and Mode of Administration, Lot Number:			
Reference Therapy	Dose	Mode of Administration	Finishing Sublot Number
Lansoprazole capsule	30 mg	oral	772812E21
Placebo	not applicable	intravenous	78-175-JT, 80-175-JT
Duration of Dosing:	Once daily for 14 days (7 days oral followed by 7 days IV)		
Criteria for Evaluation:			
Pharmacodynamics			
The primary pharmacodynamic variables analyzed were BAO and pentagastrin-stimulated MAO results obtained at 21 hours after the last dose of IV lansoprazole (Study Day 15) as compared to 21 hours after the last dose of oral lansoprazole (Study Day 8).			
The secondary pharmacodynamic variables analyzed were BAO and MAO results obtained 21 hours after the first dose of IV lansoprazole (Study Day 9) versus those obtained 21 hours after the last dose of oral lansoprazole (Study Day 8), and the BAO and MAO results obtained 21 hours after the last dose of IV lansoprazole (Study Day 15) versus those obtained 21 hours after the first dose of IV lansoprazole (Study Day 9). On Study Day 15, the differences between the last IV lansoprazole dose and last IV placebo dose were compared.			
Safety:			
Safety evaluations included adverse event assessments, clinical laboratory evaluations, vital signs, physical examinations, routine ophthalmic examination (visual acuity and funduscopic examinations), 12-lead ECG, and IV infusion site assessments.			

Best Possible Copy

Best Possible Copy

Statistical Methods:

Pharmacodynamics

BAC and MAO data were summarized for Study Day 8, prior to dosing on Study Day 9, and on the morning of Study Day 15 utilizing descriptive statistics including median, mean, standard deviation and quartiles. A comparison of BAC and MAO between Study Day 15 (evaluating the last dose of IV administration) and Study Day 8 (evaluating the last dose of oral administration) was performed. If the ratio of the population average for IV lansoprazole to that of oral lansoprazole was less than 120%, the two dosage forms would be considered to be therapeutically equivalent. The null hypothesis (H_0) of the test was specified as the population average for BAC and MAO of IV lansoprazole being greater than or equal to 120% of the parameter for oral lansoprazole (i.e., $IV \geq 1.2 \times PO$). For each subject administered IV lansoprazole in Period 2, the difference defined by subtracting 1.2 times the Study Day 8 (last oral) value from the Study Day 15 (last IV) value was obtained. Clearly, the data exhibited substantial deviation from normality. As per protocol plan, a nonparametric one-sided Wilcoxon signed-rank test was performed on these differences to assess the equivalence on the basis of BAC and MAO. Non-inferiority was concluded if the null hypothesis was rejected at a significance level of 0.05.

Safety

The number and percentage of subjects reporting adverse events were tabulated by Coding Symbols for Nomenclature of Adverse Reaction Terms III (COSTART) and body system with a breakdown by route of administration (oral or IV) and treatment (lansoprazole or placebo). Laboratory values outside reference ranges were flagged and evaluated for clinical significance. Vital signs, physical examinations, routine ophthalmic examination (visual acuity and funduscopic examinations), 12-lead ECG and injection site assessments were summarized appropriately.

Summary/Conclusions:

Pharmacodynamic Results

This study demonstrated that 7 days of treatment with IV lansoprazole was therapeutically equivalent to oral lansoprazole in the ability to suppress gastric acid output. As expected, replacing oral lansoprazole with placebo led to a loss of gastric inhibition by the seventh day.

Among the 62 subjects with available data, after 7 days of oral treatment with lansoprazole the median BAC was 0.89 mEq/hour. When subjects were then treated with IV lansoprazole for 7 days, the corresponding median BAC was improved to 0.51 mEq/hour (N=55). Among the 54 subjects with available data on both days, the difference between IV and 120% of oral BAC values was marginally significantly less than zero despite showing an improvement in median BAC with IV lansoprazole. The null hypothesis of IV lansoprazole being inferior to oral lansoprazole was not rejected at a 0.05 significance level due to a larger than expected variability in BAC. Thus, equivalency between the oral and IV lansoprazole (Study Days 8 and 15, respectively) treatment groups was not established for BAC. Nonetheless, the dissimilarity between the oral and IV lansoprazole was considered small and the p-value was approaching significance.

Among the subjects with available data, after 7 days of oral treatment with lansoprazole and 7 days of IV lansoprazole treatment the median MAO was 7.21 mEq/hour (N=61) and 7.64 mEq/hour (N=56), respectively. Among the 55 subjects with available data on both days, the difference between IV and 120% of oral MAO values was statistically significantly less than zero and the null hypothesis of IV lansoprazole being inferior to oral lansoprazole was rejected at a 0.05 significance level. Therefore, equivalency between the oral and IV lansoprazole was established for MAO.

Safety Results

As expected in this two-period study with multiple invasive procedures during the double-blind period (insertion of NG tubes, IV infusions, pentagastrin injections, etc.), the incidence of treatment-emergent adverse events was greater among subjects in the IV placebo (47%; 9/19) and IV lansoprazole 30 mg (40%; 25/62) treatment groups than in the oral lansoprazole 30 mg treatment group (5%; 4/87).

Safety Results (continued)

The most frequently reported treatment-emergent adverse events included headache (16%) in the IV placebo group and pharyngitis (15%) in the IV lansoprazole 30 mg treatment group. The pharyngitis events in the IV treatment groups all had alternative etiologies of insertion of NG tube or upper respiratory tract infection or virus. The one case of pharyngitis in the oral lansoprazole 30 mg treatment group had an alternative etiology of viral infection. The majority of adverse events reported during both treatment periods were considered mild in severity. There were no severe adverse events reported.

There were no definitely treatment-related adverse events. Five subjects (2 IV placebo and 3 IV lansoprazole 30 mg) reported seven adverse events (1 dyspepsia, 2 abdominal pain, 2 diarrhea, 1 injection site pain, 1 rash) that were considered possibly or probably treatment-related. These adverse events were mild or moderate in severity and resolved during the study.

No subject died or reported a serious adverse event during the study. One subject prematurely discontinued from the study after completion of 7 days of treatment with oral lansoprazole 30 mg and 4 days with IV lansoprazole 30 mg due to a mild rash that was considered to have a probable relationship to study drug administration. A second subject was prematurely discontinued from the study after completion of 7 days of treatment with oral lansoprazole 30 mg and 7 days with IV lansoprazole 30 mg, but before the final BAO/MAO procedure, due to increased moderate cough and pharyngitis that were considered unrelated to study drug administration.

Over the entire study, abnormal infusion site assessments were observed for 2 (11%) subjects who received IV placebo and 2 (3%) subjects who received IV lansoprazole 30 mg. All abnormalities were reported as adverse events.

No clinically important changes were observed in the analyses of laboratory or vital signs results. Physical examination findings were generally unremarkable. No clinically significant changes in ECG or fluoroscopy results were observed.

Conclusions

This study demonstrated that 7 days of treatment with IV lansoprazole was therapeutically equivalent to oral lansoprazole in the ability to suppress gastric acid output after 7 days. As expected, replacing oral lansoprazole with placebo led to a loss of gastric acid inhibition by the seventh day.

Furthermore, the 30 mg oral and 30 mg IV formulations of lansoprazole were equivalent in suppressing pentagastrin-stimulated (MAO) gastric acid output after 7 days of treatment in subjects with erosive esophagitis. For H. pylori, IV lansoprazole was more effective, as demonstrated by a trend of improvement from oral to IV lansoprazole at suppressing gastric output at steady-state. The dissimilarity between the oral and IV lansoprazole was considered small and the result was approaching significance. Lansoprazole was well tolerated. Thus, short-term (7 days) use of IV lansoprazole is an alternative to oral therapy in erosive esophagitis subjects who are unable to take oral lansoprazole capsule.

Date of the Report: 7 November 2002

Best Possible Copy

Table 11.4a Summary of BAO/MAO Results Following the Last IV Lansoprazole Dose and the Last Oral Lansoprazole Dose in Lansoprazole Study M01-308

	Lansoprazole 30 mg		p-Value†
	Last Day Oral (Study Day 8)	Last Day IV (Study Day 15)	
Median BAO	0.89 mEq/hr	0.51 mEq/hr	0.059
Median MAO	7.31 mEq/hr	7.64 mEq/hr	0.002

† Wilcoxon signed-rank test.

The data summarized in this table show that the criteria for equivalence for BAO after the last IV administration and the last oral administration was not quite met; in addition, the equivalence of the last IV administration and the last oral administration for MAO was established since the null hypothesis that they differed by more than 20% was rejected.

Cross-Reference: Statistical Tables 14.2 . 2.1 and 14.2 . 2.2

Table 11.4b Summary of BAO/MAO Results Following the First IV Lansoprazole Dose and the Last Oral Lansoprazole Dose in Lansoprazole Study M01-308

	Lansoprazole 30 mg		p-Value†
	Last Day Oral (Study Day 8)	First Day IV (Study Day 9)	
Median BAO	0.89 mEq/hr	0.64 mEq/hr	<0.001
Median MAO	7.31 mEq/hr	8.19 mEq/hr	0.037

† Wilcoxon signed-rank test.

The data summarized in this table show the criteria for equivalence of the first IV administration and the last oral administration for BAO and MAO since the null hypothesis that they differed by more than 20% was rejected ($p < 0.05$).

Cross-Reference: Statistical Tables 14.2 . 2.1 and 14.2 . 2.2

Table 11.4c Summary of BAO/MAO Results Following the Last IV Lansoprazole Dose and the First IV Lansoprazole Dose in Lansoprazole Study M01-308

	Lansoprazole 30 mg		p-Value†
	First Day IV (Study Day 9)	Last Day IV (Study Day 15)	
Median BAO	0.64 mEq/hr	0.51 mEq/hr	0.314
Median MAO	8.19 mEq/hr	7.64 mEq/hr	<0.001

† Wilcoxon signed-rank test.

The data summarized in this table show that the criteria for equivalence for BAO after the last IV administration and the first IV administration was not established with statistical significance; however, the equivalence of the last IV administration and the first IV administration for MAO was established since the null hypothesis that they differed by more than 20% was rejected.

Cross-Reference: Statistical Tables 14.2 . 2.1 and 14.2 . 2.2

Best Possible Copy

Appears This Way
On Original

Appendix 3

Cover Sheet and OCPB Filing/Review Form

Appears This Way
On Original

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission			
	Information		Information
NDA Number	21-566		Brand Name
OCPB Division (I, II, III)	II		Generic Name
Medical Division	GI		Drug Class
OCPB Reviewer	Tien-Mien Chen		Indication(s)
OCPB Team Leader	Suresh Doddapaneni		Dosage Form
			Dosing Regimen
Date of Submission	12/23/2002		Route of Administration
Estimated Due Date of OCPB Review	9/15/2003		Sponsor
PDUFA Due Date	10/23/2003		Priority Classification
Division Due Date	9/23/2003		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	x	1		M95-306
multiple dose:	X	2		Studies M01-307 & M96-486
Patients-				
single dose:				
multiple dose:	1	1		M01-308
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	(1) Is pharmacokinetic/pharmacodynamic data obtained via intravenous route supports the proposed dosage regimen relative to the available information for the currently marketed oral delayed release capsules?			
Other comments or information not included above	Sponsor currently markets oral delayed release capsules. The current application for the intravenous product relies on the data for the oral product (NDA 20-406). The three included studies obtained PK and PD (acid suppression) data from oral versus IV cross over studies in healthy volunteers.			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tien-Mien Chen
9/16/03 04:46:15 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
9/17/03 07:37:09 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-566	Brand Name	Prevacid
OCPB Division (I, II, III)	II	Generic Name	Lansoprazole
Medical Division	GI	Drug Class	Proton Pump Inhibitor
OCPB Reviewer	Suliman Alfayoumi	Indication(s)	GERD associated with EE
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Parenteral solution
		Dosing Regimen	30 mg intravenously over 30 minutes every day for up to 7 days
Date of Submission	12/23/2002	Route of Administration	Intravenous
Estimated Due Date of OCPB Review	9/15/2003	Sponsor	TAP Pharmaceuticals
PDUFA Due Date	10/23/2003	Priority Classification	Standard
Division Due Date	9/23/2003		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		M95-306
multiple dose:	X	2		Studies M01-307 & M96-486
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		
Fiability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	(1) Is pharmacokinetic/pharmacodynamic data obtained via intravenous route supports the proposed dosage regimen relative to the available information for the currently marketed oral delayed release capsules?			
Other comments or information not included above	Sponsor currently markets oral delayed release capsules. The current application for the intravenous product relies on the data for the oral product (NDA 20-406). The three included studies obtained PK and PD (acid suppression) data from oral versus IV cross over studies in healthy volunteers.			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Suresh Doddapaneni
2/8/03 10:02:16 AM
BIOPHARMACEUTICS