CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-428

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-428
Brand Name:	Prevacid® Solutab
Generic Name:	Lansoprazole delayed-release orally disintegrating tablets
Dosage form and Strength:	Oral tablets, 15 and 30 mg
Route of administration:	Oral (Place on the tongue)
Indication:	Variety of GI disorders related to gastric acid secretion (gastric and duodenal ulcer, GERD, etc.)
Sponsor:	TAP Pharmaceutical Products Inc.
Type of submission:	Original NDA
Clinical Division:	HFD-180/Gastrointestinal and Coagulation Drug Products
OCPB Division:	HFD-870/DPE II
Priority:	Standard
Submission date:	10/30/01 (original); 02/20/02; 03/05/02; 04/11/02; 04/12/02; 04/26/02; 06/20/02 (food effect study and *in vitro* stability data), 07/11/02 (Response to FDA Information Requests)
OCPB Consult date:	11/15/01
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Suresh Doddapaneni, Ph.D.

I. Executive Summary

Enteric-coated formulations for lansoprazole, a proton pump inhibitor (PPI), had been developed and approved under NDA 20-406 [Prevacid® (Lansoprazole) Delayed-Release Capsules] and NDA 21-281 [Prevacid® (Lansoprazole) Delayed-Release Oral Suspension]. The capsules and suspension are to be taken before eating (due to food effect). NDA 21-428 is for a new enteric-coated formulation, Prevacid Solutab (lansoprazole delayed-release orally disintegrating tablets), for patients who have difficulty swallowing capsules. Prevacid Solutab is formulated to disintegrate in the mouth (on the tongue) in 30-60 seconds without chewing or taking with water. Prevacid Solutab has 2 strengths, 15 and 30 mg tablets. The recommended daily dose for adults is one 15 or 30 mg Prevacid Solutab tablet QD for the different indications.

On 10/30/01, Tap Pharmaceuticals submitted data from 9 pharmacokinetic (PK) studies. On 06/20/02, the sponsor further submitted a food effect study plus additional *in vitro* stability and recovery data. Of the 10 studies submitted, four were reviewed thoroughly [two pivotal

bioequivalence (BE) studies, one study to determine the effect of co-administration of water on PK of tablet, and one food effect study]. The other six PK studies are not the subject of approval of this NDA, therefore, they were not thoroughly reviewed. There were no clinical efficacy and safety trials employing Prevacid Solutab 15 or 30 mg tablets to support this NDA.

The two pivotal single-dose, 2x2 crossover BE studies used the to-be-marketed (TBM) delayed-release orally disintegrating tablet formulation. Study **M98-948** compared Prevacid Solutab 15 mg tablet (Test) vs. the currently marketed Prevacid 15 mg capsule (Reference) in 60 healthy male and female subjects under fasting conditions and similarly, Study **M98-948** compared 30 mg Solutab tablet (Test) vs. 30 mg capsules (Reference). In the above BE studies, water was not taken with the tablet or after tablet disintegration, while capsules were administered with 180 ml of water.

The results of the two pivotal BE studies showed that both 15 and 30 mg Prevacid Solutab tablets were bioequivalent to the currently marketed Prevacid capsules. The oral disintegration times (on the tongue) were (mean ± standard deviation, SD) 48.4 ± 19.4 seconds for 15 mg tablets and 53.4 ± 21.5 seconds for 30 mg tablets. An audit of the two pivotal BE study sites conducted by the Division of Scientific Investigation (DSI) concluded that the above 2 pivotal BE studies are acceptable for Agency review. The PK study **M99-070** demonstrated bioequivalence when Prevacid Solutab 30 mg tablets (TBM formulation) were given with or without water.

Due to considerable differences in formulation between Prevacid Solutab tablet and Prevacid capsules, a single-dose, 2x2 crossover food effect study (**M02-421**) using Prevacid Solutab 30 mg tablets (the same biobatch) in 36 healthy male and female volunteers was conducted to address the food effect after the submission of this NDA. The results showed significant food effect on Prevacid Solutab, i.e., mean C_{max} (73% ↓) and $AUC_{0-\infty}$ (52% ↓). In line with the previous products, the tablet should be taken before eating.

The approved *in vitro* drug release method for capsules was used for tablet formulation as well. The proposed drug release method and specifications are adequate.

Alternative administration options were proposed [redacted] Stability data submitted was limited and inadequate, therefore, it did not support the above instructions.

Assay method that was used previously was employed in this NDA for determination of plasma lansoprazole levels and the assay method was reviewed and found acceptable.

Recommendation:

OCPB is of opinion that NDA 21-428 for Prevacid Solutab 15 and 30 mg tablets is acceptable provided that a satisfactory agreement is reached on language in the package insert (PI). Comments (1 and 2) should be conveyed to the sponsor. For Comment 2, please see detailed OCPB labeling comments in Appendix (Section V.1; page 15).

Comments to the Sponsor: (Need to be conveyed to the sponsor)

1. [redacted]

2. Changes proposed by the Agency to the package insert should be incorporated.

Date of CPB Briefing (07/31/02): Drs. H. Gallo-Torres, G. Della'Zanna, N. Nair, H. Malinowski, S. Doddapaneni, and S. Al-Fayoumi and Mr. J. Hunt

APPEARS THIS WAY
ON ORIGINAL

07/19/02
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Suresh Doddapaneni, Ph.D. 07/26/02

FT initialed by Suresh Doddapaneni, Ph.D. 08/07/02

cc: NDA 21-428, HFD-180 (H. Gallo-Torres, M. Furness), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski).

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

On 10/30/01 and 06/20/02, Tap Pharmaceutics submitted 10 PK study reports.

- Two pivotal single-dose, 2x2 crossover BE studies used the TBM formulation (Formulation II) and compared Prevacid Solutab 15 mg tablet (Test) vs. Prevacid 15 mg capsule (Reference) in 60 healthy male and female subjects under fasting conditions (**M98-948**) and similarly, 30 mg Prevacid Solutab tablet (Test) comparing Prevacid 30 mg capsules (Reference; **M98-949**).
- A PK study compared Prevacid Solutab (Formulation II) with or without water (**M99-070**) under fasting conditions in 24 healthy male subjects.
- A food effect study (**M02-421**) used 30 mg tablets (biobatch, Formulation II) given under fasting and fed conditions in 36 healthy male and female subjects.
- 6 PK studies: A non-pivotal/supportive study used a prototype formulation (Formulation I, **M98-972**) and **99546** and **W99547** are to be registered in UK (Formulation II) and **CPH 251**, **CPH 252**, and **CPH 253** are to be registered in Japan (Formulation III).

No clinical efficacy or safety trials employing Prevacid Solutab 15 or 30 mg tablets were conducted to support this NDA.

The results of the two pivotal BE studies showed that Prevacid Solutab tablet is bioequivalent to the currently marketed Prevacid capsules based on the Agency's acceptance criteria for log-transformed mean C_{max} and $AUC_{0-\infty}$ values. The 90% confidence intervals (CI) were within 80-125%. The time (mean ± SD) of Prevacid Solutab tablets staying on the tongue until disintegration were 48.4 ± 19.4 seconds for 15 mg tablets and 53.4 ± 21.5 seconds for 30 mg tablets. An audit of the two pivotal BE study sites was conducted by DSI upon HFD-180's request. The results of audit report (dated 04/24/02) concluded that the above two pivotal BE studies are acceptable for Agency review.

The results of PK study **M99-070** showed that Solutab 30 mg tablet when given with water and without water were bioequivalent. The non-pivotal PK study **M98-972** was not thoroughly reviewed since it used a prototype formulation I. Finally, five PK study summaries were not reviewed in detail since only study summaries were submitted and they are not the subject of the

approval of this NDA. Study **M98-972** and the above five study summaries showed comparable results and no major differences were found.

Significant food effect on Prevacid capsules was found previously and as stated in its labeling, the capsule should be taken before eating. Due to considerable differences in formulations between Prevacid Solutab tablet and Prevacid capsules, a single-dose, 2x2 crossover food effect study (**M02-421**) using Prevacid Solutab 30 mg tablets (the same biobatch of Formulation II) was conducted in 36 male and female healthy volunteers after the submission of the NDA. The results of the study showed significant food effects on Prevacid Solutab, i.e., mean C_{max} (73% ↓) and $AUC_{0-\infty}$ (52% ↓). Therefore, the tablets should be taken before eating as currently stated in the PI for Capsules.

The approved *in vitro* drug release method for capsules was used for Prevacid Solutab tablets. The above proposed dissolution methodology and the specifications (for Prevacid Solutab 15 and 30 mg tablets during the buffer stage of Q=[redacted]in 30min) are acceptable.

Alternative administration options were proposed by [redacted] Limited stability data (up to 2 hrs) submitted (in late June, 2002) support the above instructions only if used immediately. For 15 mg tablet dissolved in [redacted](pH 5-6), greater than [redacted]of drug was released in 2 hrs and for 30 mg tablets it was [redacted](in pH 4.4-4.6 [redacted]. Similar results were obtained for tablets dissolved in tap water. Acid resistance data on both **1)** the contents coming out of [redacted]and **2)** the contents coming out of the nasogastric tube [redacted], however, were not provided. As such, these alternative administration options should not be allowed until that data is submitted and evaluated by the Agency.

Finally, the analytical assay method that was used previously was employed in this NDA for determination of plasma lansoprazole levels and the assay method was reviewed and found acceptable.

IV. Question Based Review

A. General Clinical Pharmacology:

1. Do the two pivotal PK studies comparing Prevacid Solutab 15 and 30 mg tablets with Prevacid 15 and 30 mg capsules support the bioequivalence conclusion?

Yes, results obtained from Studies M98-948 (15 mg strength) and M98-949 (30 mg strength) showed BE between the Prevacid Solutab and Prevacid capsules.

The results are summarized in **Tables 1** and **2** and the mean plasma profiles are shown in **Figures 1** and **2**, respectively.

Table 1. Mean (± SD) Lansoprazole Pharmacokinetic Parameter Estimates in Healthy Male and Female Subjects given a 15-mg Dose as a delayed-release orally disintegrating tablet Formulation and a capsule Formulation in Study M98-948

Pharmacokinetic Parameter	15-mg Lansoprazole Tablet (Test Regimen)	15-mg Lansoprazole Capsule (Reference Regimen)
N	60	60
T_{max} (h)	1.8 ± 1.0	1.9 ± 0.9
C_{max} (ng/mL)	376.9 ± 182.5	486.5 ± 257.8
AUC$_t$ (ng·h/mL)	1079 ± 492.5	1175 ± 913.5
AUC$_\infty$ (ng·h/mL)	1168 ± 526.1	1235 ± 1123
$t_{1/2}$ (h)[a]	1.18 ± 0.36	1.18 ± 0.37
CL/F (L/h)	16.0 ± 6.0	29.4 ± 26.4

Figure 1. Mean Lansoprazole Plasma Concentration-Time Profiles obtained from Study M98-948 (Linear Scale)

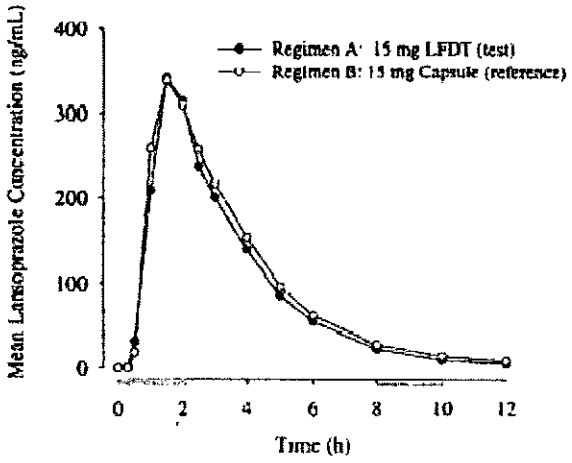
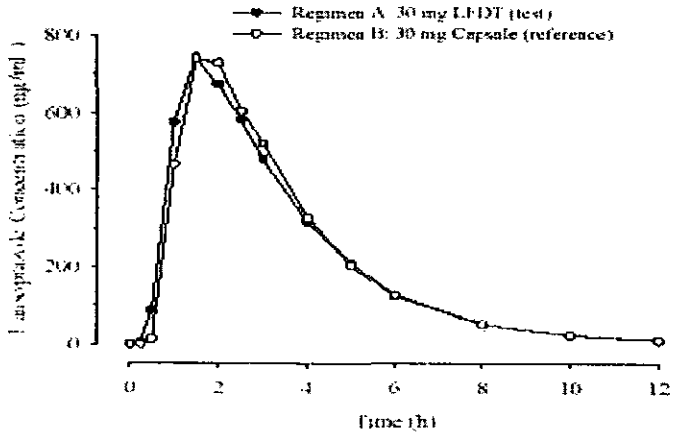


Table 2. Mean (± SD) Lansoprazole Pharmacokinetic Parameter Estimates in Healthy Male and Female Subjects Given a 30-mg Dose as a tablet Formulation II and a Capsule Formulation in Study M98-949

Pharmacokinetic Parameter	30-mg Lansoprazole Tablet (Test Regimen)	30-mg Lansoprazole Capsule (Reference Regimen)
N	59	59
T_{max} (h)	2.0 ± 1.1	2.0 ± 1.0
C_{max} (ng/mL)	1087 ± 470.3	997.2 ± 361.5
AUC_t (ng·h/mL)	2551 ± 1425	2539 ± 1181
AUC_∞ (ng·h/mL)	2597 ± 1500	2583 ± 1233
$t_{1/2}$ (h)[a]	1.18 ± 0.31	1.17 ± 0.37
CL/F (L/h)	15.2 ± 8.5	15.8 ± 14.6

Figure 2. Mean Lansoprazole Plasma Concentration-Time Profiles obtained from Study M98-949 (Linear Scale)



The 90% CI for log-transformed mean C_{max} and AUCs were within the Agency's recommended range of 0.80-1.25 for both strengths (**Table 3**).

Table 3. Bioavailability of Lansoprazole from 15-mg or 30-mg Tablet Formulation II, Relative to the Capsule Formulation, in Studies M98-948 and M98-949

	Bioavailability of Lansoprazole Tablet, Relative to Capsule Formulation			
	15-mg Strength (Study M98-948)		30-mg Strength (Study M98-949)	
Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval	Point Estimate	90% Confidence Interval
C_{max}	1.059	0.909 - 1.235	1.089	0.958 – 1.238
AUC_t	1.042	0.932 - 1.164	0.992	0.900 – 1.092
AUC_∞	1.033	0.928 - 1.150	0.988	0.900 – 1.083

The time period (mean ± SD) of the Prevacid Solutab tablet staying on the tongue (defined as the time the tablet is placed on the tongue and the time the tablet disintegrates on the tongue) was recorded to be 48.4 ± 19.4 seconds for 15 mg tablets and 53.4 ± 21.5 seconds for 30 mg tablets.

Study **M99-070** which was conducted in UK also showed that when 30 mg tablet (TBM formulation) was given with (Reference) or without (Test) water (180 ml) are bioequivalent (mean C_{max}: **0.904-1.202** and mean $AUC_{0-\infty}$: **0.915-1.089**).

B. General Biopharmaceutics:

2. What is the nature of the formulation?

The currently approved Prevacid 15 and 30 mg capsule formulations shown below in **Table 4:**

Table 4. Prevacid Capsule Formulations

Ingredient	15 mg (mg/capsule)	30 mg (mg/capsule)
Lansoprazole	15.0	30.0
Magnesium Carbonate, USP	[redacted]	
Sugar Spheres, NF		
Sucrose, NF		
Starch, NF		
Low-Substituted Hydroxypropyl Cellulose (L-HPC), NF		
Hydroxypropyl Cellulose (HPC-L), NF		
Methacrylic Acid Copolymer Dispersion		
[redacted]*, NF		
Polyethylene Glycol, NF		
Titanium Dioxide, USP		
Polysorbate 80 [redacted], NF		
Talc, USP		
Colloidal Silicon Dioxide, [redacted] NF		
Purified water**		
Total		
Capsule	***	****

*. [redacted]

**. [redacted]

***. Cap: Pink, Opaque, Body: Bluish Green Opaque #3

****. Cap: Pink, Opaque, Body: Black #1

The lansoprazole delayed-release orally disintegrating 15 and 30 mg tablet formulations (compositionally proportional) are summarized below in **Table 5** and a schematic representation of enteric coated microgranule is shown in **Figure 3**:

Table 5. Formulation II (Proposed Commercial Product)

Ingredients	15 mg (mg/15 mg tablet)	30 mg (mg/30 mg tablet)
Lansoprazole	15.0	30.0
Magnesium Carbonate USP	[redacted]	
Low-Substituted Hydroxypropyl Cellulose NF		
Hydroxypropyl Cellulose NF		
Hydroxypropyl Methylcellulose [redacted] USP		
Titanium Dioxide USP		
Talc USP		

Mannitol USP	
Methacrylic Acid Copolymer Dispersion[a] NF	
Polyacrylate . Ph Eur[b]	
Polyethylene Glycol NF	
Glyceryl Monostearate NF	
Polysorbate 80 NF	
Triethyl Citrate NF	
Ferric Oxide NF	
Citric Acid USP	
Microcrystalline Cellulose NF	
Crospovidone NF	
Strawberry	
Aspartame[c] NF	
Magnesium Stearate NF	
Purified Water [d] USP	

a.
b. Ph. Eur.: European Pharmacopeia (EP)
c.
d.

Figure 3. Schematic Representation of Enteric-coated Lansoprazole Microgranule

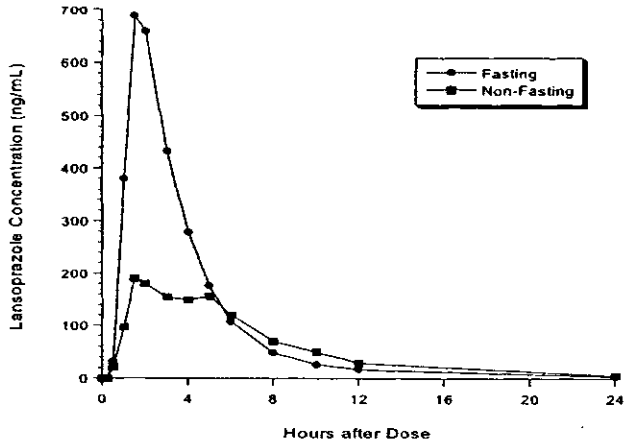
3. What is the food effect?

Significant food effect on Prevacid capsules was found previously and the PI instructs the patients to take capsule before eating. Significant food effect was also found for the orally disintegrating tablets and it should be taken before eating as well.

It was felt within the Agency that the food effect information previously collected on capsules could not be extrapolated to the delayed-release orally disintegrating tablet due to considerable differences in formulations between Prevacid Solutab tablet and Prevacid capsules. In response to Agency's query, a food effect study (**M02-421**) using Prevacid Solutab 30 mg tablets (the same biobatch) in 36 healthy male and female volunteers was conducted after the submission of this NDA. This study was a single-dose, open-label, 2x2 crossover study with a washout period of 7 days.

An FDA recommended high fat meal was employed (2 eggs fried with butter, 2stripes of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk) and the meal was consumed within 30 min prior to dosing in the fed treatment group. The above results showed significant food effects on Prevacid Solutab, i.e., mean C_{max} (73% ↓) and $AUC_{0-\infty}$ (52% ↓;**F igure 4-**).

Figure 4. Mean Plasma-Time Profiles of Prevacid Solutab 30 mg tablet given with and without a high fat meal



4. Is the proposed *in vitro* drug release method and specifications adequate for this tablet product?

Both 1) the *in vitro* drug release method for Prevacid Solutab tablets (that was employed previously for capsules) and 2) the proposed specifications in the buffer stage (Q=[redacted] in 30min) are acceptable.

The drug release methodology and proposed specifications for Solutab 15 and 30 mg tablets are shown below:

Acid Resistance:

Apparatus: USP Apparatus 2 (paddle)

Agitation: 75 rpm

Medium: 0.1N HCl, 500 mL, 37°C ± 0.5°C

Assay: [redacted]

Specification: Not More Than [redacted] in 60 minutes (USP <724>)

Drug Release (Buffer Stage):

Apparatus: USP Apparatus 2 (paddle)

Agitation: 75 rpm

Medium: pH 6.8 buffer with 5mM Sodium Dodecyl Sulfate, 900 mL, 37°C ± 0.5°C

Assay: [redacted]

Specification: Q=[redacted] in 30 minutes (USP <724>)

Mean drug release profiles in the buffer stage (from 15 min up to 60 min) of Prevacid Solutab 15 and 30 mg tablets are shown in **Figures 5** and **6.**

Figure 5. Mean (± SD) Drug Release Profiles of the Lansoprazole 15 mg Fast-Disintegrating Tablet (Biobatch # Z5133061) and the Capsule Formulations Used in Study No. M98-948

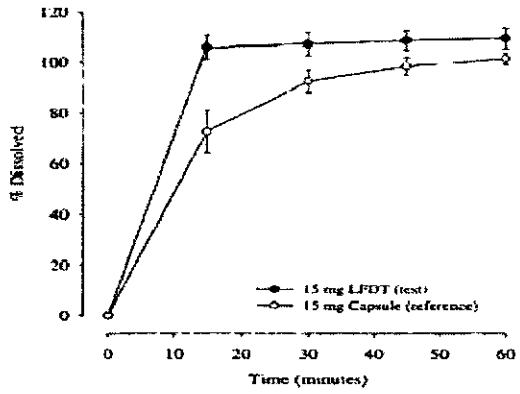
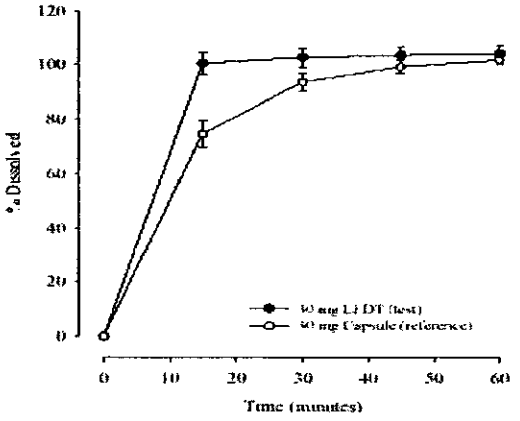


Figure 6. Mean (± SD) Drug Release Profiles of the Lansoprazole 30 mg Fast-Disintegrating Tablet (Biobatch # Z5134071) and the Capsule Formulations Used in Study No. M98-949



During the [redacted] stage (60 min): the % of lansoprazole released were 7.7 ± 0.9% and 5.8 ± 0.5 % for Solutab 15 and 30 mg biobatch tablets, respectively and those were 2.5 ± 0.4% and 1.7 ± 0.2% for Prevacid 15 and 30 mg biobatch capsules. During

the buffer stage (at 15, 30, 45, and 60 min), Prevacid Solutab 15 and 30 mg tablets all showed rapid and nearly complete dissolution in 15 min (105.8 ± 4.8% and 100.6 ± 4.0%, respectively). For Prevacid 15 and 30 mg capsules at 30 min, they were 92.3 ± 4.4% and 93.7 ± 3.5%, respectively.

For Prevacid Solutab 15 mg and 30 mg tablets, additional data at earlier time points of 5 and 10 min during the buffer stage (6 tablets per batch) were obtained upon the Agency's request and the results are shown below in **Tables 6** and **7** and **Figures 7** and **8**, respectively.

Table 6. Drug Release Profile for 15 mg Lansoprazole Tablets (Lot A1274)

Time (min)	Drug Release (%); n=6	
	Mean	SD (CV%)
5	66.2	20.2 (30.5%)
10	92.3	6.8 (7.4%)
15	99.2	1.8 (1.8%)
30	102.	1.8 (1.8%)
45	103.	1.7 (1.7%)

Figure 7. Mean Dissolution Profile for 15 mg Lansoprazole Tablets

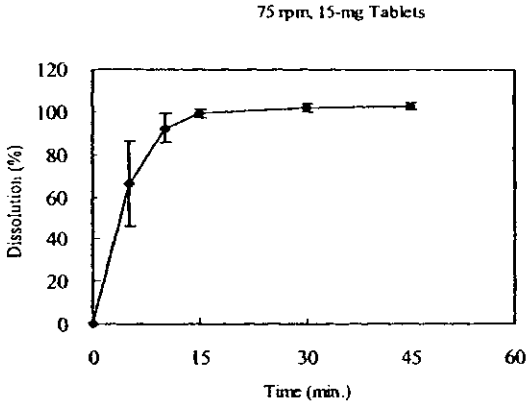
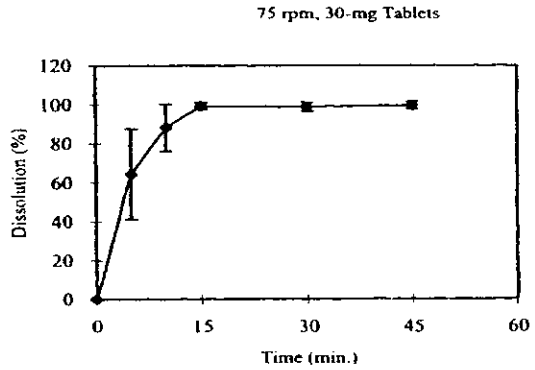


Table 7. Drug Release Profile for 30 mg Lansoprazole Tablets (Lot A1224)

Time (min)	Drug Release (%); n=6	
	Mean	SD (CV%)
5	64.5	23.3 (36%)
10	88.3	12.0 (14%)
15	99.4	1.7 (1.7%)
30	99.0	2.3 (2.3%)
45	99.7	1.9 (1.9%)

Figure 8. Mean Dissolution Profile for 30 mg Lansoprazole Tablets



5. **Are the proposed alternative administration options in the package insert adequately supported by the stability data submitted?**

   No, the stability data provided is inadequate to properly assess the alternative administration options.

C. **Analytical Methodology:**

6. **Is the analytical assay method adequately validated?**

   The assay method was reviewed and found to be satisfactory.

The results of assay method validation and study reports are shown below:

Study Number	Method	Range	LLOQ	Analytical Lab
M98-948	LC/MS/MS			
M98-949	LC/MS/MS			
M99-070	LC/MS/MS			
M02-421	LC/MS/MS			

Study Number	Assay range (ng/mL)	Standard Curve		Quality Control			
		Recovery (%)	Coefficient of Variation (%)	Intraday Variation (%)	Interday Variation (%)	Recovery (%)	Coefficient of Variation (%)
Assay							
M98-948							
M98-949							
M99-070							
M02-421							

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V. Appendices

1. Proposed Labeling (06/18/02 version) and Detailed OCPB Labeling Comments

33 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

2. *In Vitro* Stability and Recovery Data (Submitted on 06/20/02)

I. Stability Data:

Time (min)	15 mg Tablets				30 mg Tablets			
			Tap Water				Tap Water	
0 (Control)	pH	Mean (± SD)	pH	Mean (± SD)	pH	Mean (± SD)	pH	Mean (± SD)
	[redacted]	7.7 (0.4)	[redacted]	7.7 (0.4)	[redacted]	6.1 (0.4)	[redacted]	6.1 (0.4)
15		7.5 (0.6)		7.1 (0.9)		-----		6.0 (0.7)
30		8.1 (0.7)		6.9 (0.3)		5.7 (0.3)		6.2 (0.6)
60		7.6 (1.5)		6.4 (1.6)		5.9 (1.0)		8.3 (0.5)
120	[redacted]	**54.2 (1.6)**	[redacted]	**23.7 (6.6)**	[redacted]	**20.0 (1.8)**	[redacted]	**25.6 (0.8)**

II. Recovery Data:

[redacted]

Note: Acid resistance data on both **1)** the contents coming out of the [redacted] and **2)** the contents coming out of the nasogastric tube (in combination with [redacted]) were <u>not</u> provided. As such, these alternative administration options should <u>not</u> be allowed until that data is submitted and evaluated by the Agency.

3. Individual Study Reviews

Summary

Title: Bioavailability of Lansoprazole after Administration of 15 mg Lansoprazole Fast-Disintegrating Tablets (LFDT) *versus* 15 mg Lansoprazole Capsules (Protocol M98-948)

Objective: The objective of this study was to compare the bioavailability of lansoprazole after administration of one 15 mg lansoprazole fast-disintegrating tablet (test regimen) to that of one 15 mg lansoprazole capsule (reference regimen).

Drug Formulations: Characteristics of the lansoprazole fast-disintegrating tablet and the capsule formulations used in this study are listed in the following table.

	Formulation	
	Test	Reference
Strength (mg)	15	15
Dosage Form	Fast-Disintegrating Tablet	Capsule
Bulk Product Lot Number	Z5133061	638432E21
Manufacturing Site†	Takeda, Ireland	Takeda, Japan
Manufacturing Date	June 2000	March 13, 2000
Batch size	[redacted] tablets	[redacted] capsules
Potency (% of Label Claim)	[redacted]	[redacted]

† Takeda = Takeda Chemical Industries Limited.

Study Design and Dose Administration: This was a Phase I, single-dose, open-label, randomized, two-period, crossover, single-center study. In Regimen A, one 15 mg lansoprazole fast-disintegrating tablet (test regimen) was placed directly on the tongue and allowed to disintegrate completely, without chewing or swallowing the intact tablet. In Regimen B, one 15 mg lansoprazole capsule (reference regimen) was administered with 180 mL of water. Each formulation was administered after a minimum of a 10-hour fast. A washout interval of seven days separated the doses of the two study periods.

Study Site and Investigator: This study was conducted at Parkway Research Center in North Miami Beach, FL. The investigator was Marc Saltzman, M.D. Dosing was accomplished between March 20 and 30, 2001.

Subjects: Healthy adult male and female subjects (N = 60; 33 males and 27 females) were enrolled in and completed the study. Of the 60 subjects who completed the study, 47 were Caucasian/Hispanic, 7 were Caucasian, 3 were Black/Hispanic and 3 were Black. The mean age was 36.1 years (range: 19 to 55 years), the mean weight was 74.3 kg (range: 49 to 101 kg) and the mean height was 166.9 cm (range: 147.5 to 188.5 cm).

Sample Collection: Blood samples (7 mL) were collected by venipuncture into appropriately-labeled [redacted] prior to dosing (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after dosing in each study period.

Analytical Methodology: Plasma concentrations of lansoprazole were determined using a validated liquid chromatography assay method with [redacted] at [redacted] The lower limit of quantitation was [redacted] ng/mL using a [redacted] plasma sample. Samples were analyzed between the dates of April 11, 2001 and May 1, 2001.

Pharmacokinetic and Statistical Analyses: The pharmacokinetic parameters of lansoprazole were calculated using noncompartmental methods. These included: T_{max}, C_{max}, the elimination rate constant (λ), half-life ($t_{½}$), the area under the plasma concentration-time curve from time zero to time of the last measurable concentration (AUC_t), the area under the plasma concentration-time curve from time zero to infinity (AUC_∞) and apparent oral clearance (CL/F).

Analyses of variance (ANOVAs) with fixed effects for sequence, cohort, sequence by cohort interaction, period, regimen, period by cohort interaction, and regimen by cohort interaction and with a random effect for subject nested within sequence by cohort combination were performed for T_{max}, λ and the natural logarithms of C_{max}, AUC_t, and AUC_∞. Within the framework of the ANOVA, Regimen A was compared to Regimen B with a significance level of 0.05 for each comparison.

The bioavailability of Regimen A relative to that of Regimen B was assessed by the two one-sided tests procedure *via* 90% confidence intervals. Bioequivalence between the test Regimen A and the reference Regimen B was concluded if the 90% confidence

intervals from analyses of the natural logarithms of C_{max}, AUC_t, and AUC_∞ were within the 0.80 to 1.25 range.

Results: The data for the 60 subjects who received both Regimens A and B were included in the analyses. The mean ± SD pharmacokinetic parameters of lansoprazole after administration of the two regimens are shown in the following table.

Pharmacokinetic Parameters	Regimen£ A Fast-Disintegrating Tablet	Regimen£ B Capsule
N	60	60
T_{max} (h)	1.8 ± 1.0	1.9 ± 0.9
C_{max} (ng/mL)	470.9 ± 182.5	486.5 ± 257.8
AUC_t (ng•h/mL)	1079 ± 492.5	1175 ± 913.5
AUC_∞ (ng•h/mL)	1108 ± 526.4	1235± 1123
$t_{½}$ (h)‡.$	1.18 ± 0.36	1.18 ± 0.37
CL/F (L/h)+	16.0 ± 6.0	20.4 ± 26.4

£ Regimen A: 15 mg lansoprazole fast-disintegrating tablet (test).
Regimen B: 15 mg lansoprazole capsule (reference).
‡ Harmonic mean ± pseudo standard deviation.
$ Evaluations of $t_{½}$ were based on statistical tests for λ.
+ Parameter was not tested statistically.

For the two one-sided tests procedure based on analyses of log-transformed C_{max}, AUC_t, and AUC_∞, the 90% confidence intervals for evaluating bioequivalence and the corresponding point estimates of relative bioavailability are shown in the following table.

Regimens£ Test *vs.* Reference	Pharmacokinetic Parameters	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate†	Relative Bioavailability 90% Confidence Interval
A *vs.* B	C_{max}	434.6	410.2	1.059	0.909 – 1.235
	AUC_t	990.2	950.4	1.042	0.932 – 1.164
	AUC_∞	1014	981.2	1.033	0.928 – 1.150

£ Regimen A: 15 mg lansoprazole fast-disintegrating tablet (test).
Regimen B: 15 mg lansoprazole capsule (reference).
* Antilogarithm of the least squares means for logarithms.
† Antilogarithm of the difference (test minus reference) between the least squares means for logarithms.

Conclusions: The 15 mg test lansoprazole fast-disintegrating tablet (Regimen A) is bioequivalent to the 15 mg reference lansoprazole capsule (Regimen B) because the 90% confidence intervals for evaluating bioequivalence with respect to C_{max}, AUC_t, and AUC_∞ are contained within the 0.80 - 1.25 range.

Figure 1. Mean Lansoprazole Plasma Concentration-Time Profiles (Linear Scale)

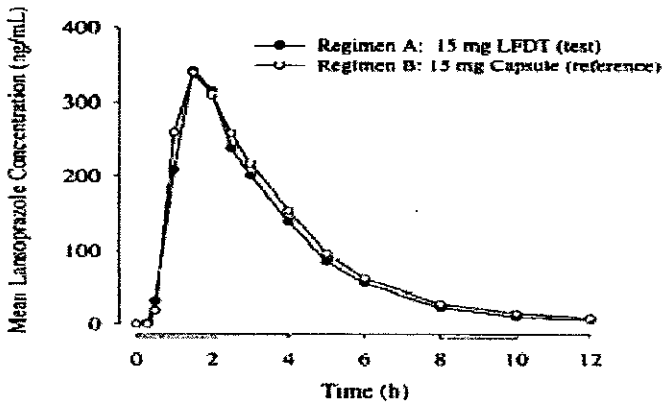
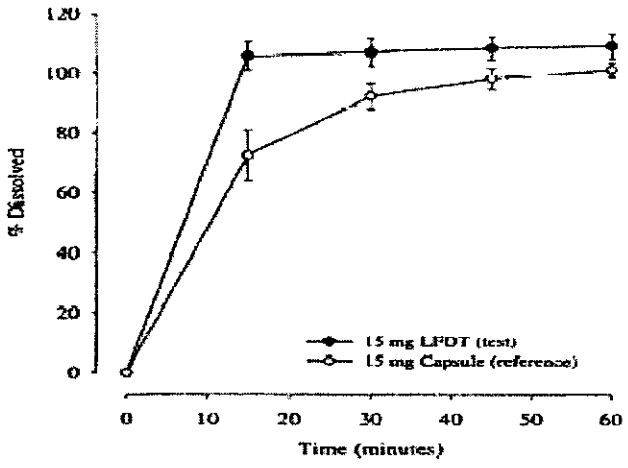


Figure 2. Mean (± SD) Dissolution Profiles of the Lansoprazole 15 mg Fast-Disintegrating Tablet and the Capsule Formulations Used in Study M98-948



Summary

Title: Bioavailability of Lansoprazole after Administration of 30 mg Lansoprazole Fast-Disintegrating Tablets (LFDT) *versus* 30 mg Lansoprazole Capsules (Protocol M98-949)

Objective: The objective of this study was to compare the bioavailability of lansoprazole after administration of one 30 mg lansoprazole fast-disintegrating tablet (test regimen) to that of one 30 mg lansoprazole capsule (reference regimen).

Drug Formulations: Characteristics of the lansoprazole fast-disintegrating tablet and the capsule formulations used in this study are listed in the following table.

	Formulation	
	Test	Reference
Strength (mg)	30	30
Dosage Form	Fast-Disintegrating Tablet	Capsule
Bulk Product Lot Number	Z5134071	671692E21
Manufacturing Site†	Takeda, Ireland	Takeda, Japan
Manufacturing Date	June 2000	August 2000
Batch size	[redacted] tablets	[redacted] capsules
Potency (% of Label Claim)	[redacted]	[redacted]

† Takeda = Takeda Chemical Industries Limited.

Study Design and Dose Administration: This was a Phase I, single-dose, open-label, randomized, two-period, crossover, single-center study. In Regimen A, one 30 mg lansoprazole fast-disintegrating tablet (test regimen) was placed directly on the tongue and allowed to disintegrate completely, without chewing or swallowing the intact tablet. In Regimen B, one 30 mg lansoprazole capsule (reference regimen) was administered with 180 mL of water. Each formulation was administered after a minimum of a 10-hour fast. A washout interval of seven days separated the doses of the two study periods.

Study Site and Investigator: This study was conducted at Parkway Research Center in North Miami Beach, FL. The investigator was Marc Saltzman, M.D. Dosing was accomplished between April 20 and May 1, 2001.

Subjects: Healthy adult male and female subjects (N = 60; 32 males and 28 females) were enrolled in and completed the study. One female subject was excluded from the pharmacokinetic analyses. Of those 59 subjects who completed the study and were included in the pharmacokinetic analyses, 50 were Caucasian/Hispanic, three were Caucasian, three were Black/Hispanic, two were West Indian and 1 was Black/West Indian. The mean age was 36.5 years (range: 18 to 55 years), the mean weight was 71.9 kg (range: 47 to 96 kg) and the mean height was 164.4 cm (range: 140.5 to 182 cm).

Sample Collection: Blood samples (7 mL) were collected by venipuncture into appropriately-labeled [redacted] prior to dosing (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after dosing in each study period.

Analytical Methodology: Plasma concentrations of lansoprazole were determined using a validated liquid chromatography assay method with [redacted], at [redacted] The lower limit of quantitation was [redacted] ng/mL using a [redacted] plasma sample. Samples were analyzed between the dates of May 14, 2001 and July 18, 2001.

Pharmacokinetic and Statistical Analyses: The pharmacokinetic parameters of lansoprazole were calculated using noncompartmental methods. These included: T_{max}, C_{max}, the elimination rate constant (λ), half-life ($t_{½}$), the area under the plasma concentration-time curve from time zero to time of the last measurable concentration (AUC_t), the area under the plasma concentration-time curve from time zero to infinity (AUC_∞) and apparent oral clearance (CL/F).

Analyses of variance (ANOVAs) with fixed effects for sequence, cohort, sequence by cohort interaction, period, regimen, period by cohort interaction, and regimen by cohort interaction and with a random effect for subject nested within sequence by cohort combination were performed for T_{max}, λ and the natural logarithms of C_{max}, AUC_t, and AUC_∞. Within the framework of the ANOVA, Regimen A was compared to Regimen B with a significance level of 0.05 for each comparison.

The bioavailability of Regimen A relative to that of Regimen B was assessed by the two one-sided tests procedure *via* 90% confidence intervals. Bioequivalence between the test Regimen A and the reference Regimen B was concluded if the 90% confidence intervals from analyses of the natural logarithms of C_{max}, AUC_t, and AUC_∞ were within the 0.80 to 1.25 range.

Results: The data for the 59 subjects who received both Regimens A and B were included in the analyses. The mean ± SD pharmacokinetic parameters of lansoprazole after administration of the two regimens are shown in the following table.

Pharmacokinetic Parameters	Regimen£ A Fast-Disintegrating Tablet	Regimen£ B Capsule
N	59	59
T_{max} (h)	2.0 ± 1.1	2.0 ± 1.0
C_{max} (ng/mL)	1087 ± 470.3	997.2 ± 361.5
AUC_t (ng•h/mL)	2551 ± 1425	2539 ± 1181
AUC_∞ (ng•h/mL)	2597 ± 1500	2583± 1233
$t_{½}$ (h)‡,$	1.18 ± 0.34	1.17 ± 0.37
CL/F (L/h)+	15.2 ± 8.5	15.8 ± 14.6

£ Regimen A: 30 mg lansoprazole fast-disintegrating tablet (test).
Regimen B: 30 mg lansoprazole capsule (reference).
‡ Harmonic mean ± pseudo standard deviation.
$ Evaluations of $t_{½}$ were based on statistical tests for λ.
\+ Parameter was not tested statistically.

For the two one-sided tests procedure based on analyses of log-transformed C_{max}, AUC_t, and AUC_∞, the 90% confidence intervals for evaluating bioequivalence and the corresponding point estimates of relative bioavailability are shown in the following table.

Regimens£ Test *vs.* Reference	Pharmacokinetic Parameters	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate†	Relative Bioavailability 90% Confidence Interval
A *vs.* B	C_{max}	976.2	896.2	1.089	0.958 – 1.238
	AUC_t	2230	2249	0.992	0.900 – 1.092
	AUC_∞	2261	2290	0.988	0.900 – 1.083

£ Regimen A: 30 mg lansoprazole fast-disintegrating tablet (test).
Regimen B: 30 mg lansoprazole capsule (reference).
* Antilogarithm of the least squares means for logarithms.
† Antilogarithm of the difference (test minus reference) between the least squares means for logarithms.

Conclusions: The 30 mg test lansoprazole fast-disintegrating tablet (Regimen A) is bioequivalent to the 30 mg reference lansoprazole capsule (Regimen B) because the 90% confidence intervals for evaluating bioequivalence with respect to C_{max}, AUC_t, and AUC_∞ are contained within the 0.80 - 1.25 range.

Figure 1. Mean Lansoprazole Plasma Concentration-Time Profiles (Linear Scale)

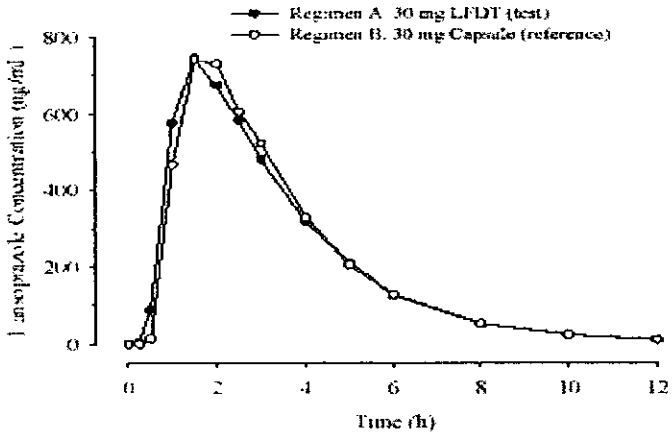
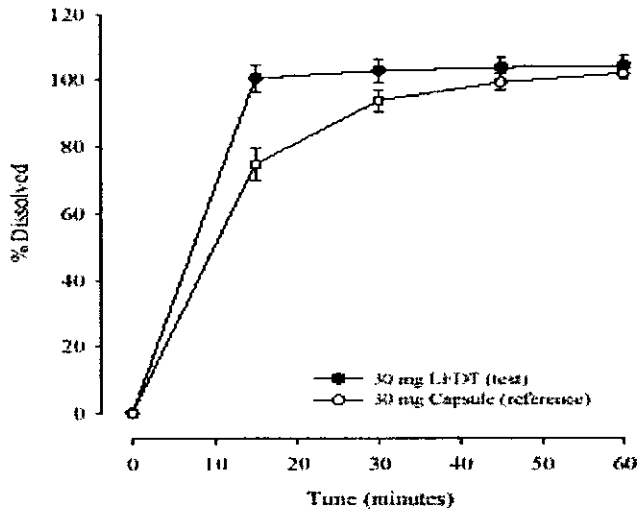


Figure 2. Mean (± SD) Dissolution Profiles of the Lansoprazole 30 mg Fast-Disintegrating Tablet and the Capsule Formulations Used in Study M98-949



Summary

Title: Bioavailability of Lansoprazole after Administration of Lansoprazole 30 mg QD Fast Dissolving Tablets (Protocol M99-070)

Objective: The objective of this study was to compare the bioavailability of a lansoprazole 30 mg fast dissolving tablet administered with and without water to the bioavailability of an intact lansoprazole 30 mg capsule administered with water.

Drug Formulations: Characteristics of the lansoprazole formulations used in this study are listed in the following table.

	Formulation	
	Fast Dissolving Tablet (Test)	Capsule (Reference)
Strength (mg)	30	30
Bulk Product Lot Number	Z5134016	G0573B
Manufacturing Site†	Takeda	Takeda
Manufacturing Date	June 1999	May 11, 1998
Batch size (#)	[redacted] Tablets	NA
Potency (% of Label Claim)	[redacted]	[redacted]

† Takeda Chemical Industries Limited, Osaka, Japan.
NA: Not Available.

Study Design and Dose Administration: This was a Phase I, single-dose, open-label, fasting, randomized, three-period, crossover, single-center study. In Regimen A, one 30 mg lansoprazole fast dissolving tablet was administered directly on the tongue. After it disintegrated, 180 mL of water was used for rinse and swallow. In Regimen B, one 30 mg lansoprazole fast dissolving tablet was administered directly on the tongue with no water administered. In Regimen C, one 30 mg lansoprazole capsule was administered orally with 180 mL of water. Each dose was administered after a minimum of a 12-hour fast and 3 hours prior to breakfast. The lansoprazole 30 mg capsule formulation served as the reference formulation in this study. A washout interval of at least 5 days separated the doses of consecutive study periods.

Study Site and Investigator: The study was conducted at Charterhouse Clinical Research Unit of Stamford Hospital (Ravenscourt Park, London, United Kingdom).

The investigator was Jorg Taubel, M.D. Dosing was accomplished on September 29, October 7, and October 14, 1999.

Subjects: Healthy adult male subjects (N=24) were enrolled in the study, with all 24 subjects completing all three periods of the study. Of the 24 subjects included in the pharmacokinetic analyses, 21 were Caucasian and three were of other races. The mean age was 23.7 years (range: 19 to 33 years), the mean weight was 73.3 kg (range: 61.2 to 87.4 kg) and the mean height was 179.0 cm (range: 165.0 to 189.0 cm).

Sample Collection: Blood samples (7 mL) were collected by venipuncture into _____ prior to dosing (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after the dose in each study period.

Analytical Methodology: Plasma concentrations of lansoprazole were determined using a validated liquid chromatography assay method _____ at _____ The lower limit of quantitation was ____ ng/mL using a ____ plasma sample. Samples were analyzed between the dates of November 10, 1999 and November 30, 1999.

Pharmacokinetic and Statistical Analyses: The pharmacokinetic parameters of lansoprazole were calculated using noncompartmental methods. These included: T_{max}, C_{max}, the elimination rate constant (β), half-life ($t_{½}$), the area under the plasma concentration-time curve from time zero to the time of the last measurable concentration (AUC_t) and the area under the plasma concentration-time curve from time zero to infinity (AUC_∞).

Analyses of variance (ANOVAs) with fixed effects for sequence, period, regimen, and with a random effect for subject nested within sequence were performed for T_{max}, β and the natural logarithms of C_{max}, and AUC_∞. Within the framework of the ANOVA, Regimen B was compared to Regimen A and each of these test regimens was separately compared to reference Regimen C with a significance level of 0.05 for each comparison.

The bioavailabilities of Regimens A and B relative to that of Regimen C, and Regimen B relative to that of Regimen A were assessed by the two one-sided tests procedure *via*

90% confidence intervals. Bioequivalence between a test regimen and a reference regimen was concluded if the 90% confidence intervals from analyses of the natural logarithms of C_{max} and AUC_{∞} were within the 0.80 to 1.25 range.

Results: All available data for the 24 subjects were included in the analyses. The mean ± SD pharmacokinetic parameters of lansoprazole after administration of each of the three regimens are shown in the following table.

	Regimens£		
Pharmacokinetic Parameters	A Test Tablets (N = 24)	B Test Tablets (N = 24)	C Reference Capsules (N = 24)
T_{max} (h)	2.1 ± 0.8*	1.7 ± 0.8	1.8 ± 0.7
C_{max} (ng/mL)	859.2 ± 389.6	893.8 ± 348.5	952.0 ± 345.9
AUC_t (ng•h/mL)+	2038 ± 1377	2072 ± 1366	2190 ± 1583
AUC_{∞} (ng•h/mL)	2070 ± 1423	2102 ± 1403	2230 ± 1666
$t_{½}$ (h)‡,$	0.95 ± 0.25	0.97 ± 0.24	0.99 ± 0.25

£ Regimen A: One 30 mg fast dissolving tablet administered with water.
Regimen B: One 30 mg fast dissolving tablet administered without water.
Regimen C: One 30 mg capsule administered with water.
+ No statistical analyses were conducted on AUC_t.
‡ Harmonic mean ± pseudo-standard deviation.
$ Evaluations of $t_{½}$ were based on statistical tests for β.
* Statistically significantly different from Regimen B ($p<0.05$).

For the two one-sided tests procedure based on analyses of log-transformed AUC_{∞} and C_{max}, the 90% confidence intervals for evaluating bioequivalence and the corresponding point estimates of relative bioavailability are shown in the following table.

Regimens[£] Test *vs.* Reference	Pharmacokinetic Parameters	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate[†]	Relative Bioavailability 90% Confidence Interval
A *vs.* C	C_{max} (ng/mL)	785.3	890.9	0.881	0.764 – 1.016
	AUC_{∞} (ng•h/mL)	1762	1869	0.943	0.864 – 1.029
B *vs.* C	C_{max} (ng/mL)	818.5	890.9	0.919	0.797 – 1.059
	AUC_{∞} (ng•h/mL)	1759	1869	0.941	0.863 – 1.027
B *vs.* A	C_{max} (ng/mL)	818.5	785.3	1.042	0.904 – 1.202
	AUC_{∞} (ng•h/mL)	1759	1762	0.998	0.915 – 1.089

£ Regimen A: One 30 mg fast dissolving tablet administered with water.
Regimen B: One 30 mg fast dissolving tablet administered without water.
Regimen C: One 30 mg capsule administered with water.

* Antilogarithm of the least squares means for logarithms.

† Antilogarithm of the difference (test minus reference) between the least squares means for logarithms.

Conclusions: With regard to AUC, the lansoprazole 30 mg fast dissolving tablet formulation, taken either with or without water (Regimens A and B, respectively), was equivalent to the reference 30 mg capsule formulation taken with water (Regimen C) because the 90% confidence intervals for evaluating bioequivalence were contained within the 0.80 - 1.25 range. The corresponding 90% confidence intervals for C_{max} extended just slightly below the lower limit of the bioequivalence range.

Summary

Report Title: Effect of Food on the Pharmacokinetics of Lansoprazole from 30 mg Lansoprazole Fast-Disintegrating Tablets (Protocol M02-421).

Objective: The objective of this study was to compare the oral bioavailability of the 30 mg lansoprazole fast-disintegrating tablets under fasting and non-fasting conditions in healthy adult subjects.

Study Design and Dose Administration: This was a Phase I, single-center, randomized, open-label, single dose two-period crossover study involving 36 subjects who received a single 30 mg lansoprazole fast-disintegrating tablet in each period. Eighteen subjects were randomly assigned to receive the study drug under fasting conditions in Period 1 and non-fasting conditions in Period 2. The remaining eighteen subjects received the 30 mg lansoprazole fast-disintegrating tablet in the opposite sequence of non-fasting and fasting conditions. A 7-day washout interval separated the doses in the two periods. Subjects were confined to the testing facility for approximately 41 hours in each period, starting at approximately 5:00 p.m. on Study Day –1, and continuing through completion of all study procedures on Day 2.

Clinical Investigator and Study Dates: This study was conducted at [redacted] under the direction of Aziz Laurent, M.D. The dose for Period 1 was administered on March 2, 2002, and the dose for Period 2 was administered on March 9, 2002.

Subject Selection: Thirty-six subjects between the ages of 18 and 55 years, inclusive, were to be enrolled in the study. Subjects were to be in good health, as evidenced by

medical history, physical examination, electrocardiogram, and laboratory profile and to have a body weight within ±15% of the accepted range based on height and body frame size.

Clinical Supplies: Lansoprazole used in this study was provided as 30 mg fast-disintegrating tablets (Takeda Chemical Industries, Lot No. Z5134071).

Sample Collection: In each period, venous blood samples for the determination of lansoprazole plasma concentrations were obtained in ——— within 5 minutes prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours after dose. The plasma samples were stored frozen at —— or lower until analyzed.

Analytical Method: Concentrations of lansoprazole in plasma were determined at ——— using a validated LC-MS/MS assay. The lower limit of quantitation with a — mL plasma sample was —— ng/mL. Quality control samples analyzed with the plasma samples from this study showed absolute deviations from the theoretical concentrations of ——— and coefficients of variation of ——.

Pharmacokinetic Analyses: Pharmacokinetic parameters for lansoprazole under fasting and non-fasting conditions were determined using standard noncompartmental methods. The pharmacokinetic parameters that were estimated included: the observed peak plasma concentration (C_{max}), the time to reach the observed peak concentration (T_{max}), the terminal elimination rate constant (λ_z), the half-life of the terminal elimination phase ($t_{1/2z}$), and the area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_t) and from time zero to infinity (AUC_∞).

Statistical Methods: Descriptive statistics for the lansoprazole concentrations in plasma and for the pharmacokinetic parameters of lansoprazole were computed for each regimen.

Analyses of variance (ANOVA) were performed on T_{max} and the natural logarithms of C_{max}, AUC_t and AUC_∞ using a model with effects for sequence, subjects nested within sequence, period and regimen (fasting and non-fasting). The effect for subjects was treated as random and all other effects were fixed. Within the framework of the ANOVA model, the bioavailability of lansoprazole under non-fasting conditions relative to fasting conditions was assessed by point estimates and 90% confidence intervals for the ratios of central values for C_{max}, AUC_t and AUC_∞.

Subject Demographics and Accountability: Thirty-six (36) healthy adult subjects were enrolled, and all of the subjects completed the study. After completion of the study and analysis of the plasma samples, it was determined that Subject 114 should have been discontinued due to a protocol deviation. Female subjects who had been on stable doses of oral contraceptives for at least 3 months prior to screening were allowed to participate in the study but were to maintain their drug regimen throughout the remainder of the study. Subject 114 had been on stable doses of an oral contraceptive until the day before the first dose of lansoprazole, then discontinued the oral contraceptive for the duration of the study. Subsequently, the data from this subject were excluded from all analyses. The mean age of the 35 subjects whose data were included in the descriptive statistics was 26 years (range: 18-52 years), the mean weight was 71.4 kg (range: 49.9-96.1 kg), and the mean height was 173.4 cm (range: 158.8-187.5 cm). Of the 35 subjects, 19 were White, eight were White/Hispanic, five were Black and three were Asian.

Results: Noncompartmental pharmacokinetic parameter estimates for lansoprazole from a 30 mg lansoprazole fast-disintegrating tablet are summarized in the following table.

Pharmacokinetic Parameter Estimates for Lansoprazole Following Oral Administration of a Single 30 mg Lansoprazole Fast-Disintegrating Tablet to Subjects Under Fasting and Non-Fasting Conditions in Study M02-421

Regimen		T_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_∞[a] (ng·h/mL)	$t_{1/2}$[a,b] (h)
Fasting	N[c]	35	35	35	32	32
	Mean	1.8	894.99	2344.23	2452.21	1.05
	SD	0.84	410.05	2212.17	2370.44	-
Non-fasting	N[c]	35	35	35	32	32
	Mean	3.3	280.44	1313.31	1471.69	1.57
	SD	1.8	226.93	1928.24	2354.02	-

[a] Data from Subjects 103, 104 and 117 were not included in the descriptive statistics, since these pharmacokinetic parameters could not be determined for these subjects in the non-fasting regimen.
[b] Harmonic mean
[c] Data from Subject 114 were not included in the descriptive statistics.

Lansoprazole was rapidly absorbed following oral administration of a 30 mg lansoprazole fast-disintegrating tablet under fasting conditions, with a mean T_{max} of 1.8 h. The mean lansoprazole C_{max} value was 895 ng/mL and mean AUC_t and AUC_∞ values were 2344 and 2452 ng·h/mL, respectively.

Lower plasma concentrations of lansoprazole were observed after oral administration of a 30 mg lansoprazole fast-disintegrating tablet following ingestion of a high-fat meal when compared to the fasting regimen. Ingestion of the meal resulted in a statistically significantly different and increased mean T_{max} and decreased C_{max}, AUC_t and AUC_∞ for lansoprazole when compared to dosing under fasting conditions. The harmonic mean for the lansoprazole apparent terminal elimination half-life in the non-fasting regimen (1.6 h) was somewhat greater than that observed in the fasting regimen (1.1 h).

The relative bioavailability of lansoprazole between fasting and non-fasting regimens was assessed via point estimates and 90% confidence intervals for the ratios of central values for the C_{max} and AUC of lansoprazole. The point estimates and 90% confidence intervals

for lansoprazole pharmacokinetic parameters tested are summarized in the following table.

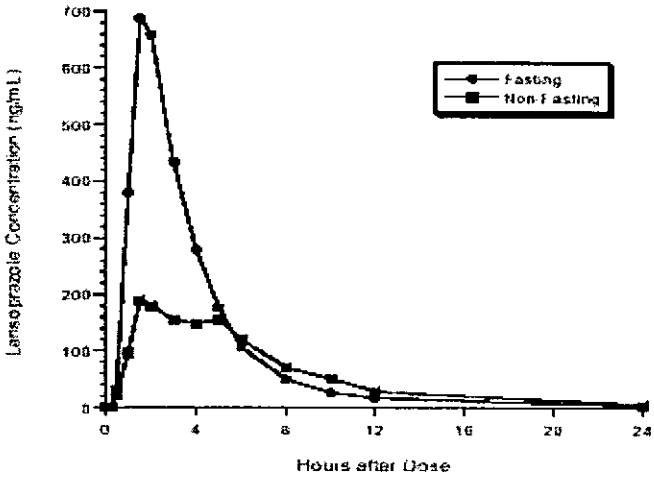
Bioavailability of Lansoprazole from a 30 mg Lansoprazole Fast-Disintegrating Tablet under Non-fasting Conditions, Relative to Fasting Conditions

Parameter	Point Estimate	90% Confidence Interval
C_{max}	0.268	0.228-0.316
AUC_t	0.455	0.400-0.517
AUC_∞	0.483	0.423-0.551

Source: Appendix D.2

Conclusions: Relative to fasting conditions, oral administration of a 30 mg lansoprazole fast-disintegrating tablet following ingestion of a high-fat meal statistically significantly delayed the mean time at which the maximum observed concentration of lansoprazole was achieved by 1.5 hours. The estimated C_{max} central value was decreased by 73% and extent of lansoprazole bioavailability (AUC_∞) was decreased by an estimated 52%. Based on these results, the 30 mg lansoprazole fast-disintegrating tablet should be taken before eating to achieve higher plasma concentrations and greater exposure (AUC) to lansoprazole.

Figure 1. **Mean Plasma Concentration-Time Profiles (Linear Format) of Lansoprazole in Healthy Subjects Following Oral Administration of a 30 mg Lansoprazole Fast-Disintegrating Tablet Under Fasting and Non-Fasting Conditions in Study M02-421**



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4. Cover Sheet and OCPB Filing /Review Form

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-428**	**Brand Name**	**Prevacid Solutab**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Lansoprazole delayed-release orally disintegration tablet**
Medical Division	**GI & Coagulation**	**Drug Class**	**Proton pump inhibitor (PPI)**
OCPB Reviewer	**Tien-Mien Chen, Ph.D.**	**Indication(s)**	**Variety of GI disorders related to gastric acid secretion**
OCPB Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Oral tablets**
		Dosing Regimen	**1 tablet QD**
Date of Submission	**10/30/01**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**08/02/02**	**Sponsor**	**Tap Pharmaceuticals**
Medical Division Due Date	**08/05/02**	**Priority Classification**	**S**
PDUFA Due Date	**08/30/02**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE	[redacted]			
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	[redacted]			
Mass balance:		0		
Isozyme characterization:		0		
Blood/plasma ratio:		0		
Plasma protein binding:		0		
Pharmacokinetics (e.g., Phase I) -	[redacted]			
Healthy Volunteers-	[redacted]			
single dose:		0		
multiple dose:		0		
Patients-	[redacted]			
single dose:		0		
multiple dose:		0		
Dose proportionality -	[redacted]			
fasting / non-fasting single dose:		0		
fasting / non-fasting multiple dose:		0		
Drug-drug interaction studies -	[redacted]			
In-vivo effects on primary drug:		0		
In-vivo effects of primary drug:		0		
In-vitro:		0		
Subpopulation studies -	[redacted]			
ethnicity:		0		
gender:		0		
pediatrics:		0		
geriatrics:		0		
renal impairment:		0		
hepatic impairment:		0		
PD:	[redacted]			
Phase 2:		0		
Phase 3:		0		
PK/PD:	[redacted]			
Phase 1 and/or 2, proof of concept:		0		
Phase 3 clinical trial:		0		
Population Analyses -	[redacted]			
Data rich:		—		
Data sparse:		—		

II. Biopharmaceutics	[redacted]			
Absolute bioavailability:		0		
Relative bioavailability -	[redacted]			
solution as reference:		0		
alternate formulation as reference:		0		
Bioequivalence studies -	[redacted]			
traditional design; single / multi dose:		3	3	**All show BE**
replicate design; single / multi dose:		0		
Food-drug interaction studies:		1	1	**Significant food effect**
Dissolution:	X			
(IVIVC):	N/A			
Bio-wavier request based on BCS	N/A			
BCS class	N/A			
III. Other CPB Studies	[redacted]	[redacted]		
Genotype/phenotype studies:		0		
Chronopharmacokinetics		0		
Pediatric development plan		0		
Literature References		0		
Total Number of Studies		10	4	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	1. Please provide the location in the NDA of the statistical printouts (similar to pages 543 and 544, Volume 1.11) for BE assessments for Study Nos. **M98-948** and **M98-949**. If not already submitted, please provide the above data to the Agency for review. 2. There is a significant food effect on the approved capsule formulation. The fast-disintegrating tablet formulation is different from the capsule formulation and therefore, the effects of food on the fast-disintegrating tablet formulation can be different. Please provide data to address this. 3. The fast-disintegrating tablets dissolved completely in [redacted] under pH 6.8 conditions. Thus, the dissolution methodology used may not be discriminatory. Please provide dissolution data in [redacted] in pH 6.8 medium, if available to support your statement (Page 88, Volume 1.10), i.e., "Earlier time points (< 15min) could not be taken because of the requirement for the slow addition of the buffer concentrate".
QBR questions (key issues to be considered)		**1. Do the two pivotal PK studies comparing Prevacid Solutab 15 and 30 mg tablets with Prevacid 15 and 30 mg capsules support the bioequivalence conclusion?** **2. What is the nature of the formulation?** **3. What is the food effect?** **4. Is the proposed *in vitro* drug release method and specifications adequate for this tablet product?** **5. Are the proposed alternative administration options in the package insert adequately supported by the stability data submitted?** **6. Is the analytical assay method adequately validated?**
Other comments or information not included above		
Primary reviewer Signature and Date		**Tien-Mien Chen, Ph.D. 08/07/02**
Secondary reviewer Signature and Date		**Suresh Doddapaneni, Ph.D. 08/07/02**

CC: NDA 21-428, HFD-850 (Electronic Entry or Lee), HFD-180 (H.Gallo-Torres, M. Furness), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski), CDR (Z. Zadeng).

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
8/8/02 10:46:50 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
8/8/02 11:07:43 AM
BIOPHARMACEUTICS