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*APPLICATION NUMBER:*  
75-311

**Bioequivalence Review(s)**

APR 15 1998

Famotidine Tablets USP  
20 mg and 40 mg  
ANDA # 75-311  
Reviewer: Kuldeep R. Dhariwal  
File name: 75311SDW.D97

Teva Pharmaceuticals  
1510 Delp Drive  
Kulpsville  
PA 19443  
Submission Date:  
December 29, 1997

## Review of Fasting and Non-Fasting Studies, Dissolution Data and Waiver Request

The firm has submitted fasting and non-fasting studies and dissolution data comparing its famotidine tablet, 40 mg with Merck's Pepcid® tablet, 40 mg. The firm has also requested for waiver of *in vivo* bioequivalence study requirements for its 20 mg tablet. To support the request, the firm has submitted comparative dissolution profiles on 20 mg test tablet and reference listed drug Pepcid®, 20 mg.

### Introduction:

Famotidine is a competitive inhibitor of histamine H<sub>2</sub>-receptors. It inhibits both diurnal and nocturnal basal gastric acid secretions elicited by histamine and other H<sub>2</sub>-antagonists in a dose-dependent, competitive manner. It also reduces gastric acid secretions stimulated by food and pentagastrin.

Famotidine is rapidly but incompletely absorbed from the GI tract after oral administration. The onset of the antisecretory effect occurred within one hour of drug administration and the maximum effect was dose-dependent, occurring within 1-3 hours. The bioavailability of oral doses is 40-45%, and is increased by food and decreased by antacids. The duration of inhibition of secretion by doses of 20 and 40 mg was 10-12 hours. Famotidine has an elimination half-life of 2.5-3.5 hours. It undergoes minimal first-pass metabolism and is eliminated, primarily as unchanged drug, in the urine.

Famotidine is currently marketed as Pepcid® (20 mg and 40 mg tablets as prescription drug) and Pepcid AC® (10 mg tablets as OTC drug) manufactured by Merck Co. Famotidine is indicated for

the relief of heartburn, acid indigestion and sour stomach.

**Bioequivalence Study under Fasting Conditions:**

**A. Objective:**

The objective of this study conducted under fasting conditions in healthy adult male volunteers is to compare the relative bioavailability of Famotidine Tablets, 40 mg of Teva with that of Pepcid® 40 mg Tablets manufactured by Merck Co.

**B. Study Sites and Investigators:**

Clinical Site: Gateway Medical Research

Clinic Director:

Principal Investigator: Thomas Christopher, M.D.

Analytical Site:

Analytical Director:

Statistics: Bioassay Laboratory

Protocol 'A relative bioavailability study of famotidine (40 mg) tablets under fasting conditions' was approved by the St. Charles Community Institutional Review Board.

Consent Form: A copy of the volunteer informed consent form used in the study is given on page 591, vol. 3.5.

Study Dates: Period I March 15, 1997

Period II March 29, 1997

Analysis Dates: May 16 to June 17, 1997

**C. Study Design:**

The study was a single-dose, randomized, two-way crossover design, with two weeks washout period between doses. The subjects were assigned to two sequences at random as follows:

Sequence	Subject number	Period I	Period II
1	1,4,6,8,10,11,16,17,19,20 21,22,23,25,27,28,31	A	B
2	2,3,5,7,9,10,12,13,14,15,18 24,26,29,30,32	B	A

A: Famotidine Tablet, 1 x 40 mg, Teva Pharmaceuticals; Lot #K-21671; Lot size                      tablets; Manufacture Date: 10/28/96; Assay: 96.1%; Content Uniformity: 97.0%.

B: Pepcid® Tablet, 1 x 40 mg, Merck; Lot #B8781; Expiration Date: June 1998; Assay: 95.7%; Content Uniformity: 94.2%.

The formulation of the test product is given in Table 1.

The subjects were housed from 12 hours prior to dosing until 16 hours post-dose. The subjects fasted for 10 hours prior to dosing until 4 hours after dose administration. The drug products were administered with 240 mL of water. No fluid was allowed from 1 hour prior to dosing until 1 hour after dosing. Subjects were served standardized meals and beverages. Meals were the same in content and quantity during each study period. Blood pressure and pulse measurements were obtained prior to dose, and at 2 and 16 hours post-dose.

#### D. Subject Selection:

Thirty-two healthy, male subjects were enrolled in the study using following inclusion criteria:

- 18-45 years of age
- no more than  $\pm 10\%$  from normal for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis within clinically acceptable limits completed within 21 days prior to period I dosing.

Subjects were excluded from this study based on the following criteria:

- history of chronic alcoholism, drug or narcotic abuse
- history of gastrointestinal, digestive, endocrine disorders
- history of malignancy, stroke, diabetes, cardiac, renal, liver disease, or other serious illness
- history of allergic responses to the class of drug being tested
- subjects who have been exposed to known hepatic enzyme inducing or inhibiting agents within 30 days

- treatment with other investigational drug during 30 days prior to this study
- subjects who used tobacco in any form within past 90 days
- blood/plasma donation within 30 days prior to study

Subjects were imposed with following restrictions:

- no prescription or OTC medications within 14 days prior to period I dosing and throughout the study
- no caffeine and/or xanthine containing products for at least 48 hours prior to dosing, and during blood sampling period
- no alcohol for at least 48 hours prior to dosing and during the periods when blood samples were obtained
- no strenuous physical activity during the confinement

#### **E. Sample Collection:**

Blood samples (10 mL) were drawn in Vacutainers with EDTA at pre-dose (0 hour) and at 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, and 16 hours. Samples were centrifuged and plasma was separated and stored at  $-20^{\circ}\text{C}$ .

#### **F. Analytical Methods: NOT TO BE RELEASED UNDER FOI**

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#### **G. Pharmacokinetics/Statistical Analysis:**

The analytical data were used to calculate the pharmacokinetic parameters:  $\text{AUC}_{0-t}$ ,  $\text{AUC}_{0-\text{inf}}$ ,  $C_{\text{max}}$ ,  $T_{\text{max}}$ , half-life, and elimination rate constant. The pharmacokinetic parameters and drug plasma concentrations were evaluated statistically by ANOVA for differences due to treatments, study days, dosing sequence, and subjects within sequence. The statistical analysis was performed using SAS software. The SAS GLM procedure was used for the analysis of variance. The study power calculations and 90% confidence interval calculations were based on the least-squares

means values generated by the SAS LSMEANS option to the SAS GLM procedure and the standard error of the estimate as given by the GLM procedure.

#### H. Results:

##### 1. Clinical:

Of the 32 subjects enrolled, 30 completed the study. Subject #12 cut his hand requiring antibiotic treatment during washout period and therefore did not complete the study. Subject #16 withdrew for personal reasons. Some subjects experienced headache, lightheadedness, nausea etc. The events were comparable on test and reference drugs.

**Protocol deviations:** All but one blood samples were collected within two minutes of scheduled time. Corrections were made in the calculations for that sample.

##### 2. Analytical: NOT TO BE RELEASED UNDER FOI

**LINEARITY:** Standard curve range 5-300 ng/mL. Correlation coefficients were greater than 0.996. The peak height ratios (y) of famotidine to internal standard and the concentrations of the standards (x) were fitted by weighted (1/y) linear least squares regression analysis to the equation:  $y=a+bx$ , where a is the y-intercept and b is slope of the standard curve.

**ACCEPTANCE CRITERIA:** A run was accepted as valid if the r value was greater than 0.99 and at least 2/3 of the QC samples were within  $\pm 20\%$  of the expected values. At least one QC sample from each concentration must be within the above criteria.

**QC SAMPLES:** 10, 60, and 250 ng/mL

<b>ACCURACY:</b> Standards	98-104%
QC samples	95.2-103%

<b>PRECISION:</b> Standards	1.9-9.6%
QC samples	3.4-10.0%

**REASSAYS:** Twelve samples were repeated due to anomalous value, three due to low standard eliminated, 2 because peaks were not

integrated, and 1 due to chromatographic interference.

LONG-TERM STABILITY: Six sets of controls at low, medium, and high QC concentrations were prepared and stored on March 26, 1997. The six replicates were analyzed on September 29, 1997. The results show that mean change for 187 days was -14.4% for 250 ng/mL, -13.3% for 60 ng/mL, and -2.7% for 10 ng/mL.

NOTE: The study samples were stored for no more than 92 days.

The firm has provided following pre-study method validation results:

LINEARITY: Standard curve range 5-300 ng/mL. Correlation coefficients were better than 0.999.

ACCURACY: Inter-day	Standards	98.5-104%
	QC samples	97.6-98.2%
Intra-day	Standards	92.3%-108%
	QC samples	94.1-103%

PRECISION: Inter-day	Standards	2.5-9.3%
	QC samples	4.4-5.2%
Intra-day	Standards	1.7-13.2%
	QC samples	2.0-5.7%

RECOVERY:	10 ng/mL	68.4%	
	60 ng/mL	69.3%	
	250 ng/mL	65.8%	
	Internal standard (Nizatidine) 4 $\mu$ g/mL		80.4%

STABILITY:

- a) Freeze-thaw: stable over 3 cycles
- b) Stability after extraction: extracted samples were left at room temperature for 48 hours and then injected. Results show that extracted samples are stable at room temperature for 48 hours.

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of famotidine at each time point after test and reference products are shown in Table 2. The time courses of famotidine after the two products are plotted in Figure 1. The pharmacokinetic parameters are summarized in Table

2. Based on least squares means,  $AUC_{0-t}$  and  $AUC_{0-inf}$  of the test product were about 7% higher than that of the reference product. The  $C_{max}$  of the test product was 5% higher compared to reference product and occurred 2 minutes earlier.

The test/reference ratios for  $AUC_{0-t}$  ranged from 0.66 to 1.91 (mean 1.11),  $AUC_{0-inf}$  ranged from 0.66 to 1.83 (mean 1.11), and for  $C_{max}$  ranged from 0.56 to 1.69 with a mean of 1.09.

The  $AUC_{0-t}/AUC_{0-inf}$  ratios ranged from 0.88 to 0.97 for test and from 0.88 to 0.98 for reference product.

### **Comments:**

1. The pharmacokinetic parameters and 90% confidence intervals were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.

2. The 90% confidence intervals for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  are within acceptable limits of 80-125%. There was no statistically significant period, sequence or treatment effect for any of these parameters.

### **Bioavailability of Famotidine Tablets Under Non-Fasting Conditions:**

#### **A. Objective:**

To compare the bioavailability of test formulation of famotidine to an equivalent dose of the reference drug (Pepcid<sup>®</sup>, Merck) in healthy male volunteers under fasting and non-fasting conditions.

#### **B. Study Sites and Investigators:**

Clinical Site: Gateway Medical Research

Clinic Director: 1

Principal Investigator: William Poggemeier, M.D.

Analytical Facility: ---

Analytical Director

Statistics: Bioassay Laboratory

Protocol #B-10096 'A limited food effect study of famotidine (40 mg) tablets' was approved by the St. Charles Community IRB.

Consent Form: A copy of the volunteer informed consent form is given on page 1496, vol. 1. 5.

Study Dates: March 12, 1997

March 19, 1997

March 26, 1997

Analysis Dates: July 16 to August 23, 1997

### C. Study Design:

This study was designed as a randomized, three treatment, three-periods study with a wash-out period of 7 days. Eighteen healthy, male subjects were enrolled in the study. Subjects were housed from 10 hours prior to dosing until after the 16 hour blood draw. Subjects were assigned as follows:

Subject #	Period I	Period II	Period III
9,12,17	A	B	C
3,6,18	B	C	A
1,8,16	C	A	B
4,11,14	A	C	B
5,7,15	B	A	C
2,10,13	C	B	A

A= Famotidine tablet, 1x40 mg, Teva Pharmaceuticals; Lot #K-21671; administered after a 10 hour fast

B= Famotidine tablet, 1x40 mg, Teva Pharmaceuticals; Lot #K-21671; administered after a standard breakfast

C= Pepcid® tablet, 1x40 mg, Merck; Lot #B8781; administered after a standard breakfast

Lot numbers of drug products administered in this study are the same as those used for the fasting study.

### D. Subject Selection:

Eighteen subjects were enrolled in the study with essentially same inclusion and exclusion criteria as in the fasting study. They were subjected to same screening procedure and restrictions.

## E. Study Procedure:

Treatment A: Subjects were given a single oral dose of the assigned formulation with 240 mL of water after a fast of at least 10 hours.

Treatments B and C: Subjects were given a standardized breakfast 30 minutes before dosing after a fast lasting at least 10 hours. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 2.45 ounces of hash brown potatoes, 180 mL of orange juice, and 240 mL of whole milk. All subjects completed their entire meal. The dose was given with 240 mL of water. All subjects fasted for 4 hours after dosing.

## F. Sample collection, Analytical Methods, and Pharmacokinetics/ Statistical Analysis:

Same as in fasting study.

## G. Results:

### 1. Clinical:

Of the 18 subjects enrolled in the study, 16 completed the study. Subject #1 had an ear infection requiring antibiotic treatment between period I and II. Subject #14 elected to withdraw in period I after 1.5 h of dosing due to feeling lightheaded and uncomfortable with the blood draws. Two subjects complained of headaches on test drug.

**Protocol deviations:** All blood samples were drawn within 2 minutes of their scheduled times except one sample which was 3 minutes late.

### 2. Analytical:

LINEARITY: Standard curve range 5-300 ng/mL  
Correlation coefficients were greater than 0.999.

QC SAMPLES: 10, 60, and 250 ng/mL

ACCURACY: Standards            97.1-103%

QC samples 96.2-99.1%

PRECISION: Standards 1.1-7.2%  
QC samples 4.1-11.8%

REASSAYS: Ten samples were repeated due to anomalous value, nineteen due to chromatographic interference, and one due to no internal standard. All samples of subject #12 were repeated due to chromatographic interference.

LONG-TERM STABILITY: Six sets of controls at low, medium, and high QC concentrations were prepared and stored on March 26, 1997. The six replicates were analyzed on September 29, 1997. The results show that mean change for 187 days was -14.4% for 250 ng/mL, -13.3% for 60 ng/mL, and -2.7% for 10 ng/mL.

NOTE: The study samples were stored for no more than 162 days.

### 3. Pharmacokinetics/Statistics:

The mean plasma concentrations of famotidine measured at each sampling time is given in Table 3. The time courses of famotidine concentrations after the three treatments are given in Figure 2. The pharmacokinetic parameters and ratios of means are given in Table 4.

**Comparison of test and reference products after a meal:** The least squares (LS) means for  $AUC_{0-t}$  and  $AUC_{0-inf}$  of the test and reference products were almost the same. The LS means for  $C_{max}$  of the test product was 2% higher than that of the reference product and occurred almost at the same time (Table 4).

**Comparison of test product given after a meal vs. given under fasting conditions:** The LS means for  $AUC_{0-t}$  and  $AUC_{0-inf}$  given after a meal were about 12 and 13% lower compared to that of the same product given under fasting conditions. The LS means for  $C_{max}$  given after a meal was 11% lower and occurred 24 minutes later when compared to that of the same product given under fasting conditions (Table 4).

The individual subject test non-fasting/reference non-fasting ratios for  $AUC_{0-t}$  ranged from 0.715-1.224,  $AUC_{0-inf}$  ranged from 0.795 to 1.214, and for  $C_{max}$  ranged from 0.719-1.245.

The  $AUC_{0-t}/AUC_{0-inf}$  ratios ranged from 0.80 to 0.95 for test non-fasting, from 0.88 to 0.96 for test fasting, and from 0.85 to 0.96 for reference non-fasting.

**Comments:**

1. The pharmacokinetic parameters and ratios of means were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.
2. Ratios of means for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  between test non-fasting and reference non-fasting are within the acceptable limits of 0.80-1.20. The non-fasting study is acceptable.

**In Vitro Dissolution Testing:**

The firm has submitted comparative dissolution data for test and reference products using USP method. The dissolution testing was done in 900 mL 0.1M monobasic potassium phosphate buffer, pH 4.5 using apparatus II (paddle) at 50 rpm. The dissolution profiles of test and reference tablets are similar. The test products dissolve more than in 30 minutes and meet the specifications (Table 5).

**Waiver Request:**

The firm is requesting for a waiver of *in vivo* bioequivalence study for its 20 mg famotidine tablets. The 20 mg tablets are proportionally similar in their active and inactive ingredients to 40 mg tablets (Table 1). The dissolution profiles on 20 mg tablets are acceptable. The waiver can be granted.

**Recommendations:**

1. The bioequivalence study submitted under fasting conditions by Teva Pharmaceuticals on its famotidine tablet, 40 mg, lot #K-21671 comparing it to Pepcid®, 40 mg tablet, lot #B8781 manufactured by Merck has been found acceptable to the Division of Bioequivalence. The study demonstrates that Teva Pharmaceutical's famotidine tablet, 40 mg is bioequivalent to the reference product, Pepcid® 40 mg tablet manufactured by Merck.

2. The bioequivalence study submitted under non-fasting conditions by Teva Pharmaceuticals on its famotidine tablet, 40 mg, lot #K-21671 comparing it to Pepcid®, 40 mg tablet, lot #B8781 manufactured by Merck has been found acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Teva Pharmaceutical's famotidine tablet, 40 mg is similar to that of the reference product, Pepcid® 40 mg tablet manufactured by Merck.

3. The dissolution testing conducted by the firm on its famotidine tablets 20 mg and 40 mg is acceptable. The formulation for 20 mg test tablet is proportionally similar to the 40 mg strength of the test product which underwent bioequivalency testing. The waiver of the *in vivo* bioequivalence study requirements for 20 mg tablets of the test product is granted. The 20 mg test tablets are therefore deemed bioequivalent to Pepcid® 20 mg tablets, manufactured by Merck.

4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.1M monobasic phosphate buffer at 37°C using apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

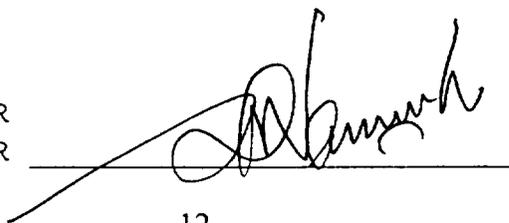
Not less than : the labeled amount of famotidine in the dosage form is dissolved in 30 minutes.

5. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

M. Dhariwal. 4/13/98

Kuldeep R. Dhariwal, Ph.D.  
Review Branch II  
Division of Bioequivalence

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FT INITIALED S. NERURKAR



Date 4/13/98

Concur: Dale P. Conner Date 4/15/98  
Dale P. Conner, Pharm. D.  
Director  
Division of Bioequivalence

Draft: 4/10/98

TABLE 2

MEAN PLASMA FAMOTIDINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS  
IN FASTING STUDY (n=30)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.24	1.34	0.26	1.41	0.94
0.5	23.07	16.31	16.62	15.54	1.39
0.75	54.92	19.15	40.61	25.30	1.35
1	74.27	22.56	64.65	30.05	1.15
1.5	89.25	30.64	84.92	26.20	1.05
2	99.20	34.83	92.03	25.90	1.08
2.5	100.76	34.99	93.78	26.62	1.07
3	96.44	34.77	91.09	25.63	1.06
3.5	90.27	30.13	86.01	24.66	1.05
4	86.53	28.28	83.01	27.23	1.04
5	70.96	24.79	70.35	21.49	1.01
6	54.70	18.05	52.56	16.58	1.04
8	34.06	11.65	31.26	9.71	1.09
10	19.88	6.44	18.75	5.91	1.06
12	12.12	4.57	11.13	4.56	1.09
14	7.58	3.79	7.27	3.98	1.04
16	4.14	3.73	3.73	3.67	1.11

UNIT: PLASMA LEVEL=NG/ML TIME=HRS  
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	683.43	196.06	642.30	170.31	1.06
AUCT	651.77	194.63	611.30	170.32	1.07
CMAX	108.40	35.43	102.56	27.70	1.06
KE	0.24	0.05	0.24	0.04	1.00
LAUCI	657.92	0.28	616.62	0.31	1.07
LAUCT	625.21	0.29	583.96	0.33	1.07
LCMAX	103.09	0.32	98.35	0.31	1.05
THALF	3.08	0.80	3.05	0.65	1.01
TMAX	2.32	0.76	2.35	0.85	0.99

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR  
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE  
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	683.43	642.30	1.06	97.68	115.13
AUCT	651.77	611.30	1.07	97.74	115.49
CMAX	108.40	102.56	1.06	96.53	114.86
LAUCI	657.92	616.62	1.07	97.82	116.38
LAUCT	625.21	583.96	1.07	97.91	117.07
LCMAX	103.09	98.35	1.05	95.78	114.73

TABLE 3

MEAN PLASMA FAMOTIDINE LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY (n=16)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	0.43	1.73	0.40	1.61	0.00	0.00	1.07
0.5	20.32	8.24	5.80	8.57	3.95	5.94	3.51
0.75	48.94	15.76	19.21	16.15	17.25	16.12	2.55
1	67.63	23.26	36.72	24.74	33.77	24.84	1.84
1.5	81.61	35.28	57.26	26.04	55.69	29.04	1.43
2	81.86	40.14	68.84	30.42	65.91	23.55	1.19
2.5	76.46	34.94	70.88	27.65	72.29	21.31	1.08
3	74.56	37.78	70.31	26.74	72.23	18.69	1.06
3.5	69.64	29.95	66.59	22.52	68.38	19.44	1.05
4	66.43	26.33	64.34	22.10	62.94	17.33	1.03
5	56.08	19.55	52.04	19.48	52.94	17.60	1.08
6	42.58	14.62	41.25	16.35	41.75	15.37	1.03
8	26.99	9.11	26.31	11.54	25.94	10.27	1.03
10	16.59	6.29	15.60	7.09	15.45	6.12	1.06
12	9.23	4.99	9.92	4.50	9.79	4.47	0.93
14	6.03	4.54	5.95	4.70	6.27	4.17	1.01
16	3.66	4.00	3.27	4.03	2.36	3.71	1.12

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS  
 MEAN PLASMA FAMOTIDINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.25	.	.
0.5	5.15	1.47
0.75	2.84	1.11
1	2.00	1.09
1.5	1.47	1.03
2	1.24	1.04
2.5	1.06	0.98
3	1.03	0.97
3.5	1.02	0.97
4	1.06	1.02
5	1.06	0.98
6	1.02	0.99
8	1.04	1.01
10	1.07	1.01
12	0.94	1.01
14	0.96	0.95
16	1.55	1.38

1= TEST FASTING  
 2= TEST NON-FASTING  
 3= REFERENCE NON-FASTING

TABLE 4

FAMOTIDINE ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY (N=16)

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	560.01	198.41	501.51	156.02	500.07	137.71	1.12
AUCT	521.73	194.55	463.88	153.77	460.24	131.51	1.12
CMAx	88.11	39.70	80.42	28.50	77.96	20.52	1.10
KE	0.22	0.07	0.22	0.05	0.21	0.06	1.02
LAUCI	535.59	0.29	481.78	0.29	484.13	0.26	1.11
LAUCT	496.76	0.30	442.91	0.31	444.67	0.26	1.12
LCMAx	81.59	0.39	75.98	0.35	75.56	0.26	1.07
THALF	3.42	1.05	3.43	1.22	3.76	2.01	1.00
TMAx	2.19	1.15	2.59	0.71	2.59	0.84	0.84

(CONTINUED)

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR  
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE  
 ARITHMETIC MEANS AND RATIOS

PARAMETER	RMEAN13	RMEAN23
AUCI	1.12	1.00
AUCT	1.13	1.01
CMAx	1.13	1.03
KE	1.04	1.02
LAUCI	1.11	1.00
LAUCT	1.12	1.00
LCMAx	1.08	1.01
THALF	0.91	0.91
TMAx	0.84	1.00

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR  
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE  
 LSMEANS AND RATIOS

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	570.78	508.65	510.84	1.12	1.12	1.00
AUCT	532.88	471.02	471.39	1.13	1.13	1.00
CMAx	90.28	81.43	80.14	1.11	1.13	1.02
LAUCI	544.47	486.45	492.16	1.12	1.11	0.99
LAUCT	505.89	447.54	452.84	1.13	1.12	0.99
LCMAx	83.57	76.84	77.39	1.09	1.08	0.99

1= TEST FASTING  
 2= TEST NON-FASTING  
 3= REFERENCE NON-FASTING

**Table 5. In Vitro Dissolution Testing**

Drug (Generic Name): Famotidine Tablets  
 Dose Strength: 20 mg and 40 mg  
 ANDA No.: 75311  
 Firm: Teva pharmaceuticals  
 Submission Date: December 29, 1997  
 File Name: 75311SDW.D97

**I. Conditions for Dissolution Testing: USP method**

USP XXIII Basket: Paddle: x RPM: 50  
 No. Units Tested: 12  
 Medium: 0.1M phosphate buffer, pH 4.5 Volume: 900 mL  
 Specifications: in 30 minutes  
 Reference Drug: Pepcid AC (Merck)  
 Assay Methodology:

**II. Results of In Vitro Dissolution Testing:**

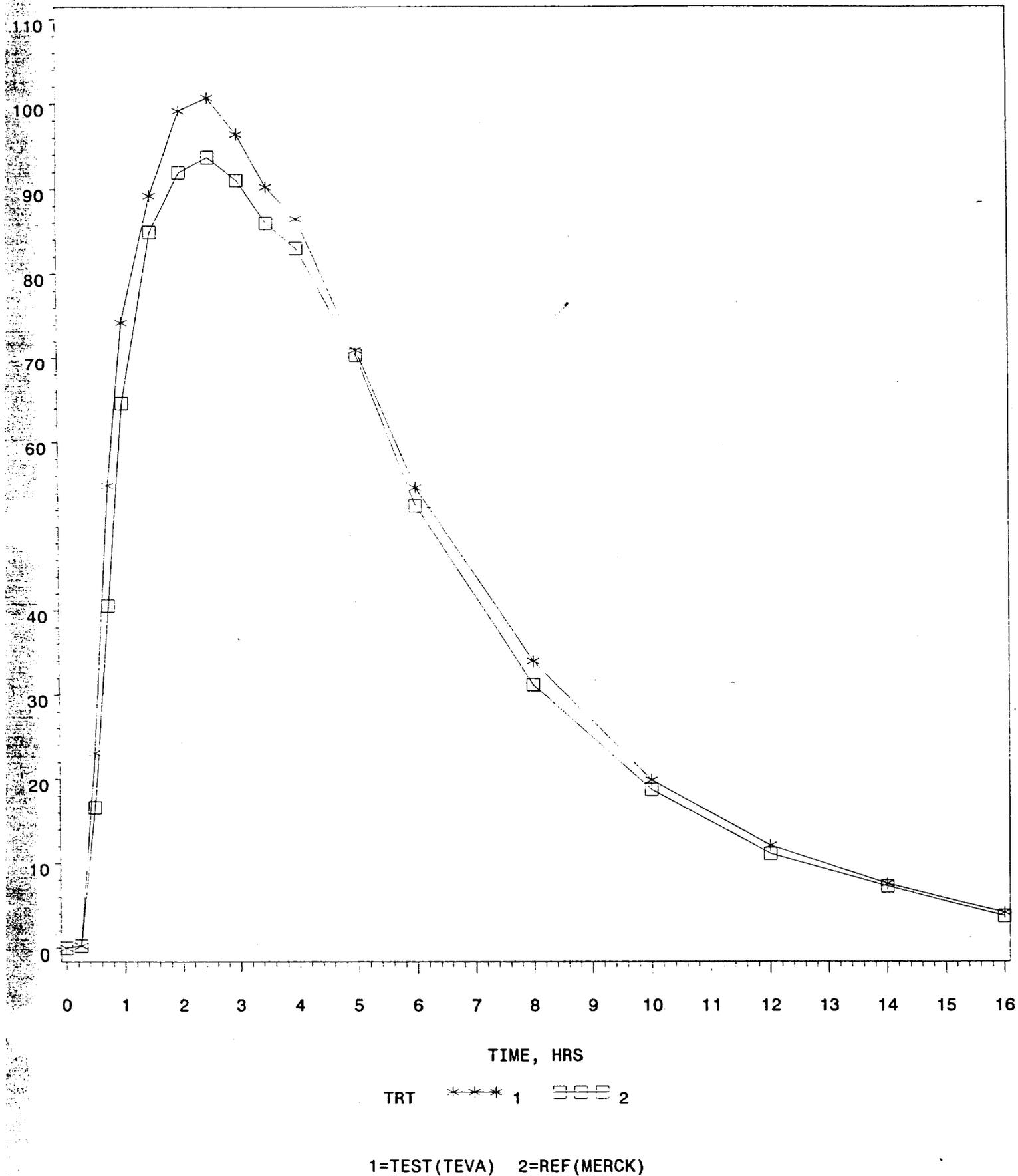
Sampling Times (Minutes)	Test Product Lot #K-21670 Strength(mg) 20			Reference Product Lot #B5105 Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	100.7		0.7	102.6		1.3
20	102.5		0.6	103.0		1.0
30	102.8		0.6	103.0		0.9

Sampling Times (Minutes)	Test Product Lot #K-21671 Strength(mg) 40			Reference Product Lot # B8781 Strength(mg) 40		
	Mean %	Range	%CV	Mean %	Range	%CV
10	97.3		1.9	98.4		0.9
20	100.7		1.5	99.3		1.1
30	101.4		0.9	99.7		1.1

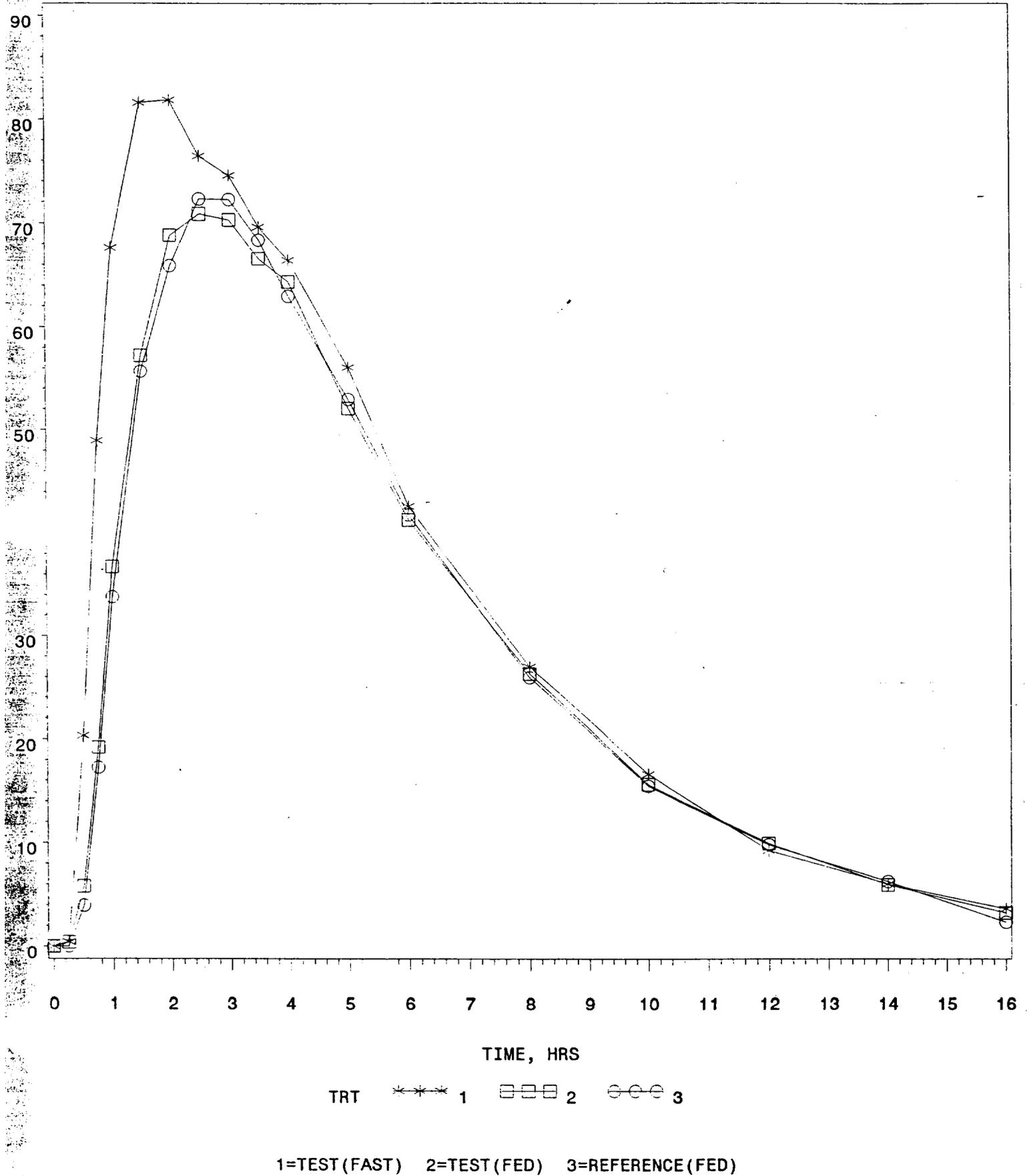
# FIG 1. PLASMA FAMOTIDINE LEVELS

FAMOTIDINE TABLETS, 40 MG, ANDA #75-311  
UNDER FASTING CONDITIONS  
DOSE=1 X 40 MG



# FIG 2. PLASMA FAMOTIDINE LEVELS

FAMOTIDINE TABLETS, 40 MG, ANDA #75-311  
UNDER FASTING/NONFASTING CONDITIONS  
DOSE=1 X 40 MG



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-311

APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Famotidine tablets, 20 mg and 40 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.  
Director  
Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research