

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75611

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

5

ANDA # : 75-611

SPONSOR : TorPharm

DRUG AND DOSAGE FORM : ^{FAMOTIDINE} Tablets STRENGTH(S) : 20 mg and 40 mg

TYPES OF STUDIES : In vivo bioequivalence studies under fasting conditions.

CLINICAL STUDY SITE(S) : ()

ANALYTICAL SITE(S) : ()

STUDY SUMMARY : The study demonstrated that under fasting conditions, TorPharm's Famotidine Tablets, 40 mg is bioequivalent to Merck's Pepcid® 40 mg.

DISSOLUTION : The dissolution data for the 40 mg and 20 mg are acceptable.

DSI INSPECTION STATUS

Inspection needed: YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>	Inspection status:	Inspection results:
First Generic <input type="checkbox"/>	Inspection requested: (date)	
New facility <input type="checkbox"/> (new analytical facility) <input checked="" type="checkbox"/> No	Inspection completed: (date)	
For cause <input type="checkbox"/>		
other <input type="checkbox"/>		

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D.

BRANCH : III

INITIAL : (/S/) DATE : 5/14/99

TEAM LEADER : Barbara M. Davit, Ph.D.

BRANCH : III

INITIAL : /S/) DATE : 5/17/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DC DATE : 5/30/99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-611

APPLICANT: TorPharm

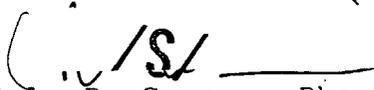
DRUG PRODUCT: Famotidine Tablets, 40 mg and 20 mg

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

The dissolution testing should 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,

for 

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

CC: ANDA #75-611
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Secretary - Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:

HFD-658/ Z. Wahba *Z.W. 5/14/99*
HFD-658/ B. Davit *BMD 5/17/99*
HFD-650/ D. Conner *for Rev 5/25/99*

BIOEQUIVALENCY - ACCEPTABLE

submission date: 03/29/99

- OK BMD* 1. **FASTING STUDY (STF)** Strengths: 40 mg
Clinical: () Outcome: AC
Analytical _____
- OK BMD* 2. **DISSOLUTION DATA** Strengths: 20 mg
Outcome: AC

OUTCOME DECISIONS: **AC** - Acceptable

WINBIO COMMENTS: Acceptable Biostudy

Famotidine

20 mg and 40 mg Tablets

ANDA #75-611

Reviewer: Z. Wahba

TorPharm

Vernon Hills, IL

Submission date:

March 29, 1999

**REVIEW OF AN IN VIVO BIOEQUIVALENCE STUDY,
DISSOLUTION DATA AND A WAIVER REQUEST**

I. OBJECTIVE:

Review the following:

1. TorPharm's in vivo bioequivalence study under fasting conditions comparing its drug product Famotidine Tablet, 40 mg to the reference listed drug Merck's Pepcid[®] tablet, 40 mg (NDA #19-462).
2. Dissolution data for the 20 mg and 40 mg strengths of test and reference drug products.

II. INTRODUCTION

Famotidine is a competitive inhibitor of histamine H₂-receptors. It inhibits both diurnal and nocturnal basal gastric acid secretions elicited by histamine and other H₂-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.

RLD: Merck's Pepcid[®] tablet, 40 mg.

Recommended dose: 40 mg once a day at bedtime.

Note (For Internal Use Only):

The Office of Generic Drugs has informed Apotex Corp. via written correspondence (letter dated 07/07/98) that a non-fasting study is not needed at the present time.

III. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER FASTING CONDITIONS
(Study Protocol #090-69-11417)

A. Study Information:

Sponsor: TorPharm, Inc.
 Clinical and Analytical Facilities:

Principal Investigator:
 Laboratory Director:
 Pharmacokineticist:

B. Treatment Plan:

Study design	Single dose, randomized, two-way crossover study under fasting conditions.
Treatment	A=Test prod. (TorPharm's Famotidine Tablet, 40 mg) B=Ref. Prod. (Merck's Pepcid® tablet, 40 mg)
Dose administered	1X40 mg
Batch\Lot #	Test= Lot #FD8069A Reference= Lot #H3022
Lot\Batch size	Test= _____ units, Ref.= not given
Content Uniformity	Test= 99.5%, Ref.= 100.4%
Assay	
Test manufacturing date (or expiration for Ref.)	Test= 09/1998, Ref.=07/2000
No. of subjects	Enrolled=26 (13 males, 12 females), completed=26 (13 males, 12 females).
Drop-outs	None
Food & Fluid Intake	Subjects fasted overnight for at least 10 hours before dosing and 5 hours after dosing. The drug products were administered with 240 mL of water at room temperature. Water was not permitted for 1 hr before and 1 hr after dosing. Standard meals were provided at appropriate times thereafter.
Clinical study dates	Period I= 10/31/98; Period II= 11/07/98
Sample analysis dates	11/13/98 to 12/07/98
Wash out period	7 days

Blood sampling	Pre-dose (0 hour) and at 0.5, 1, 1.5, 1.75, 2, 2.25, 2.5, 3, 3:5, 4, 5, 6, 8, 10, 12, 14, and 16 hours.
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C. **Adverse Events:** (volume C1.1, pages #161 and 172-173)
 Twelve subjects reported experiencing twenty-nine adverse events. Several of the events were complaints of headache were for which a physician was contacted. The majority of events resolved without medical intervention.

D. **Assay Methodology:** (NOT TO BE RELEASED UNDER FOI)
 (See volume C1.1, the Analytical Section)

Analytical method	
Analyte	
Sensitivity (LOQ)	
Linearty	
Quality control (QC) samples	
Accuracy & Precision of the QC samples	
Accuracy & Precision of the calibration curve standard	
Recovery	
Stability	

E. **IN VIVO BE STUDY & STATISTICAL ANALYSIS:**

The plasma concentrations and pharmacokinetic parameters of famotidine were analyzed using SAS-GLM procedure for analysis of variance. The following blood concentrations and pharmacokinetic parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are presented below:

Table #1
Mean Famotidine Concentrations (ng/mL)
in plasma in 26 Subjects Following a Single Oral Dose of
1X40 mg Famotidine Tablets Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	29.06	19.58	29.12	25.96	1.00
1	99.29	44.78	85.72	43.87	1.16
1.5	119.33	53.26	113.91	43.48	1.05
1.75	124.45	50.45	119.60	48.32	1.04
2	127.81	47.30	125.37	48.28	1.02
2.25	127.73	44.58	123.64	49.95	1.03
2.5	124.32	42.12	115.97	40.50	1.07
3	117.30	39.84	112.08	40.93	1.05
3.5	107.16	37.41	104.28	38.36	1.03
4	97.08	35.35	95.14	33.22	1.02
5	77.36	28.69	75.39	27.94	1.03
6	58.31	22.11	55.80	17.90	1.05
8	34.60	14.29	34.38	13.49	1.01
10	21.02	8.64	20.64	8.39	1.02
12	13.05	5.67	12.89	5.46	1.01
14	8.83	3.93	8.66	3.65	1.02
16	5.91	2.62	6.08	2.58	0.97

MEAN1=Test-Product

MEAN2=Test-Product

Table #2
Mean Pharmacokinetic Parameters (Arithmetic) for Famotidine
in 26 Subjects Following a Single Oral Dose of
1X40 Famotidine Tablets, Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	789.68	268.94	762.70	231.87	1.04
AUCT	761.51	261.68	733.25	226.38	1.04
C _{MAX}	140.70	46.58	139.70	46.31	1.01
KE	0.22	0.04	0.22	0.03	1.02
*LAUCI	748.60	0.33	733.75	0.28	1.02
*LAUCT	720.92	0.34	704.44	0.28	1.02
*LC _{MAX}	132.92	0.35	133.42	0.30	1.00
THALF	3.20	0.53	3.25	0.55	0.98
T _{MAX}	2.21	0.83	2.11	0.89	1.05

MEAN1=Test-product

MEAN2=Ref.-product

UNIT: AUC=NG.HR/ML

C_{MAX}=NG/ML

* The values represent the geometric mean (antilog of the means of the logs).

Table #3
LSMeans And The 90% Confidence Intervals
in 26 Subjects Following a Single Oral Dose of
1X40 Famotidine Tablets, Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	748.60	733.75	1.02	95.95	108.48
LAUCT	720.92	704.44	1.02	95.98	109.12
LCMAX	132.92	133.42	1.00	93.15	106.55

MEAN1=Test-product MEAN2=Ref.-product
 UNIT: AUC=NG.HR/ML CMAX=NG/ML
 LOWCI 12=Lower C.I. for T/R UPPCI12=Upper C.I. for T/R

Not: RMSE per ANOVA tables are as follow: LAUCT=0.01827740,
 LAUCI=0.01672581, LCMAX=0.02005422

Comment on the fasting study:

Under fasting conditions, the mean plasma famotidine levels for the test and reference products were comparable to each other as shown in Table #1 and Figure #1. The 90% confidence intervals for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3). The T/R mean ratios (RLSM12) for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25% (Table #3).

IV. FORMULATION COMPARISON

TorPharm's formulation for its test products, famotidine tablets, 40 mg and 20 mg are reported on page #1217, volume C1.3. A copy of the formulation statement is included in this report (Attachment #1).

V. DISSOLUTION DATA:

Method: USP 23
 Apparatus: Apparatus II (paddle) at 50 rpm
 Medium: 900 mL of 0.1M phosphate buffer pH 4.5
 Sampling times: 10, 20, 30 and 45 minutes
 Number of tablets: 12
 Test product: TorPharm's Famotidine Tablets, 40 mg (lot #FD8069) and 20 mg (lot #FD8068).
 Reference product: Merck's Pepcid® Tablets, 40 mg (lot #H3022) and 20 mg (lot #H2995).
 Specification: NLT % (Q) in 30 minutes

Results:

1. Copies of the dissolution data are included in this report (Attachments #2 and 3).
2. The dissolution comparison profiles (for all strengths) using the similarity factor (F2), are included in this report (Attachment #4-7).

Conclusion:

All famotidine tablet products tested meet the dissolution specifications [Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes]. The dissolution data for the test products are acceptable.

Comments on the dissolution data: (NOT TO BE RELEASED UNDER FOI)

The F2 values (similarity factor) for the 40 mg and 20 mg strengths of the test product are as follows:

F2 Factor		
Strengths	Test	Reference
40 mg (bio-study) vs 20 mg	F2=59.63	F2=56.81
40 mg Test bio-lot vs 40 mg Ref. Bio-lot		F2=53.24
20 mg Test vs 20 mg Ref.		F2=44.71

VI. RECOMMENDATION

1. The single dose bioequivalence study, under fasting conditions (study #090-69-11417), conducted by TorPharm on its Famotidine Tablet, 40 mg, lot #FD8069, comparing it to the reference listed drug Merck's Pepcid® tablet, 40 mg, lot #H3022, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, TorPharm's Famotidine tablets, 40 mg are bioequivalent to Merck's Pepcid® tablets, 40 mg.
2. The dissolution testing conducted by the firm on its Famotidine Tablets, 40 mg and 20 mg has been found acceptable. The formulation for the 20 mg strength is proportional to the 40 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of *in vivo* bioequivalence study requirements for the 20 mg tablets of the test product is granted. The Division of Bioequivalence deems TorPharm's Famotidine Tablet, 20 mg to bioequivalent to the reference product, Merck's Pepcid®

Tablets, 20 mg.

- The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 M Phosphate buffer, pH 4.5 as the dissolution medium with apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

ISI
Zakaria Z. Wamba, Ph.D.
Division of Bioequivalence
Review Branch III

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FT INITIALLED BDAVIT

BMD 5/14/99

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5/17/99

Concur: *ISI*

Date: *5/30/99*

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Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence