CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-712

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-712 (N-000) Famotidine 20 and 40 mg Orally Disintegrating Tablets	SUBMISSION DATE: 09/07/04 (N-000, BB)
BRAND NAME: Fluxid	
SPONSOR: Schwarz Pharma	REVIEWER: Tien-Mien Chen, Ph.D.

Addendum to the primary CPB review dated 07/13/04

At the time of completion of the primary CPB review dated 07/13/04 for the original NDA submission (N-000), the inspection report from the Division of Scientific Investigation (DSI) was not available as the inspection was not conducted yet. The CPB review concluded conditional acceptance pending an acceptable outcome of the inspection. The inspection was conducted by DSI during the week of 08/16 and a report of the inspection was finalized on 09/02/04.

According to the inspection report, form 483 citation was issued as the chromatograms in run FAM031 (related to Subject No. 14) were not integrated consistently. The PK data obtained from subject No. 14 was therefore excluded and BE was reassessed (based on 27 instead of 28 subjects) by the sponsor. The sponsor's report of reanalysis of the PK data was submitted on 09/07/04 (N-000, BB). The results of BE reassessment obtained (after excluding subject No.14) showed that Fluxid™ ODT 40 mg tablets placed on the tongue until disintegration and either swallowed without water (Treatment B; Test of interest,) or swallowed with 240 mL water (Treatment A) are still bioequivalent to the Reference (Treatment C) under fasting conditions based on the Agency's 2-1-sided BE acceptance criteria. Table 1 shows the results of the BE reanalysis.

Table 1. Results of BE Reassessment for Treatment B (Test of interest) vs. Treatment C (Reference)

NDA 21-712 for Fluxid™ (Famotidine ODT) BE Assessment					
PK Parameters Mean (SD)	**Treatment A**	**Treatment B (Test of interest)**	**Treatment C (Reference)**	**B vs. C Point Estimate**	**90% CI**
C_{max} (ng/ml)[1]	134.0 (40.1)	133.6 (38.2)	130.5 (39.9)	-----	-----
T_{max} (hr)[1]	2.41 (0.93)	2.67 (0.88)	2.22 (1.04)	-----	-----
$T_{1/2}$ (hr)	4.88 (0.67)	4.99 (0.72)	5.17 (1.03)	-----	-----
$AUC_{0\text{-last}}$[1] (ng-hr/ml)	890.4 (210.9)	873.7 (208.4)	846.7 (227.9)	-----	-----
$AUC_{0\text{-}\infty}$[1] (ng-hr/ml)	912.8 (212.9)	895.1 (208.6)	869.3 (229.5)	-----	-----
Ln (C_{max})[2]	4.853 (0.310)	4.855 (0.289)	4.833 (0.273)	102.3	94.27-111.12
Ln $(AUC_{0\text{-last}})$[2]	6.765 (0.240)	6.744 (0.252)	6.707 (0.270)	104.1	97.30-111.31
Ln $(AUC_{0\text{-}\infty})$[2]	6.790 (0.238)	6.769 (0.246)	6.734 (0.265)	103.8	97.25-110.82

[1]. Arithmetic mean (± standard deviation, SD).
[2]. Log-transformed geometric least square mean (± SD).

As such, the conclusions in the 07/13/04 CPB review are final. No further action is needed.

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/s/

Tien-Mien Chen
9/16/04 10:11:26 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
9/16/04 01:18:57 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-712
Brand Name:	Fluxid™ (famotidine orally disintegrating tablets)
Generic Name:	Famotidine
Dosage form and Strength:	Orally Disintegrating Tablets, 20 and 40 mg
Route of Administration:	Oral
Indication:	Short-term treatment and maintenance therapy related to GI disorders
Sponsor:	Schwarz Pharma
Type of Submission:	Original
Clinical Division:	GI and Coagulation (HFD-180)
OCPB Division:	HFD-870/DPE II
Priority:	Standard
Submission Date:	11/24/03, 02/16/04
OCPB Consult Date:	12/03/03
Reviewer:	Tien-Mien Chen, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.

I. Executive Summary

Currently, there is no orally disintegrating tablet (ODT) dosage form of famotidine on the market. On 11/24/03, Schwarz Pharma submitted original NDA 21-712 under 505(b)(2) seeking approval for Fluxid™ (famotidine) 20 and 40 mg ODT.

A bioequivalence (BE) study (SP701) conducted in 28 healthy male and female subjects comparing Fluxid 40 mg ODT (placed on the tongue and swallowed without water after disintegration) with the currently marketed Merck's Pepcid (famotidine) immediate release (IR) 40 mg tablet (swallowed with 240 mL water) under fasting conditions demonstrated bioequivalence (BE) of the two products. Biowaiver for the lower strength, 20 mg ODT, can be granted since both 20 and 40 mg strengths of Fluxid ODT are compositionally proportional and show similar dissolution characteristics. The proposed dosing regimen for Fluxid™ ODT is the same as Pepcid® IR tablet and there is no new indication proposed for Fluxid™ ODT.

The approved Merck's Pepcid® products have a common package insert (PI) for the suspension, tablets, and injectable formulations. Dosing for pediatric patients <1 year of age is to be done with oral suspension (allows for pediatric dosing on mg/kg basis). In pediatric patients 1-16

years of age, starting doses for peptic ulcer are 0.5 mg/kg/day p.o. at bedtime or divided b.i.d. up to 40 mg/day. In patients with GERD, the dose is 1.0 mg/kg/day p.o. divided b.i.d up to 40 mg b.i.d.

A. Recommendations

NDA 21-712 (N-000) Fluxid™ (famotidine orally disintegrating tablets) 20 and 40 mg submitted on 11/24/03 Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II is acceptable from Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the PI (p. 11 labeling comment No. 2) and dissolution specifications (below).

The proposed dissolution specifications for Fluxid™ ODT need to be tightened as follows:

NLT — (Q) in 10 minutes

B. Phase IV Commitments: None

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II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

On 11/24/03, Schwarz Pharma submitted an original NDA 21-712 under 505(b)(2) regulations seeking approval for Fluxid™ (famotidine) 20 and 40 mg ODT. One BE study was conducted comparing Fluxid™ 40 mg ODT with Merck's Pepcid IR 40 mg tablet. Comparative *In Vitro* dissolution data was also submitted. A biowaiver for the lower strength 20 mg Fluxid™ ODT has been supported by *in vitro* dissolution data using three different dissolution media. The proposed dosing regimen for Fluxid™ ODT is the same as for Pepcid IR tablet and there is no new indication.

The BE study SP701 was a randomized, single-dose, open-label, 3x3 crossover study comparing test product, Fluxid™ 40 mg ODT administered with (Treatment A) and without 240 mL water (Treatment B) vs. the reference, Pepcid 40 mg IR tablet (Treatment C) with 240 mL water under fasting conditions with a washout period of one week in 28 healthy subjects (18 males and 10 females).

The results of the BE study demonstrated that Fluxid™ 40 mg ODT is bioequivalent to the currently marketed Merck's Pepcid 40 mg IR tablet under fasting conditions based on the Agency's 2-1-sided BE acceptance criteria. The *In Vitro* dissolution comparisons also showed comparable dissolution data and profiles **1)** between Fluxid™ 40 mg ODT and Merck's Pepcid 40 mg IR and **2)** between Fluxid™ 40 mg and 20 mg ODT. Biowaiver for the lower strength of Fluxid™ 20 mg ODT can therefore be granted.

IV. Question Based Review

A. General Attributes

Merck's Pepcid® (famotidine) currently has three dosage forms on the market for prescription use, i.e., IV injectable (10 mg/mL), oral suspension (40 mg/5 mL), and IR oral tablets (20 and 40 mg). Pepcid® oral suspension allows for pediatric use from <1 to 16 years old (on mg/kg basis). Previously, Merck also had ODT dosage form in two strengths (20 and 40 mg) approved on 05/28/98 under NDA 20-752 (Pepcid® RPD), but it has been discontinued and no longer on the market.

Generic products for famotidine IV injectable injection and IR oral tablets are currently available on the market, but not for oral suspension. Pepcid AC® IR tablets (10 and 20 mg) are available as the over-the-counter (OTC) drug.

Schwarz Pharma is seeking approval for Fluxid™ (famotidine orally disintegrating tablets) 20 and 40 mg , NDA 21-712, under 505(b)(2) provisions relying on the Agency's previous findings of safety and efficacy for Merck's Pepcid® Tablets (NDA 19-462). As such, there are no proposed changes to the indications (including pediatrics) and administration schedule. In support of the NDA, a single dose BE study (SP701) comparing the approved Pepcid® Tablets 40 mg (reference) and Fluxid™ 40 mg ODT (test) was conducted. A biowaiver with supportive *in vitro* dissolution data is sought for Fluxid™ 20 mg ODT as the 20 mg and 40 mg strengths are compositionally proportional.

B. General Clinical Pharmacology

Famotidine is a competitive antagonist for histamine H_2-receptor. The primary clinically important pharmacologic activity of famotidine is inhibition of gastric secretion. In normal volunteers and hypersecretors, famotidine inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin.

As stated in the Pepcid® package insert for oral products, the onset of the antisecretory effect occurred within one hour; the maximum effect was dose-dependent, occurring within one to three hours. Duration of inhibition of secretion by doses of 20 and 40 mg was 10 to 12 hours. Single evening oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects. There was no cumulative effect with repeated doses. When famotidine was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of famotidine was raised to about 5. Famotidine had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by famotidine.

C. Intrinsic Factors: Not Applicable

D. Extrinsic Factors: Not Applicable

E. General Biopharmaceutics:

Q: Is Fluxid™ 40 mg ODT (Treatment B) bioequivalent to Pepcid® 40 mg IR tablet (Treatment C)?

The PK study SP701 was randomized, single-dose, open-label, 3x3 crossover study with a washout period of one week in 28 healthy subjects (18 males and 10 females) under fasting conditions with the following treatments:

Treatment A: Fluxid™ 1 x 40 mg ODT administered (placed on the tongue till disintegrated and then swallowed with 240 mL water)

Treatment B: Fluxid™ 1 x 40 mg ODT administered (placed on the tongue till disintegrated and then swallowed without water)

Treatment C: Pepcid® 1 x 40 mg IR tablet (swallowed with 240 mL water)

The results obtained showed that Fluxid™ ODT 40 mg tablets placed on the tongue until disintegration and either swallowed without water (Test of interest- Treatment B) or swallowed with 240 mL water (Treatment A) are bioequivalent to the Reference (Treatment C) under fasting conditions based on the Agency's 2-1-sided BE acceptance criteria as shown below in Table 1:

Table 1. Results of BE Assessment for Treatment B (Test of interest) vs. Treatment C (Reference)

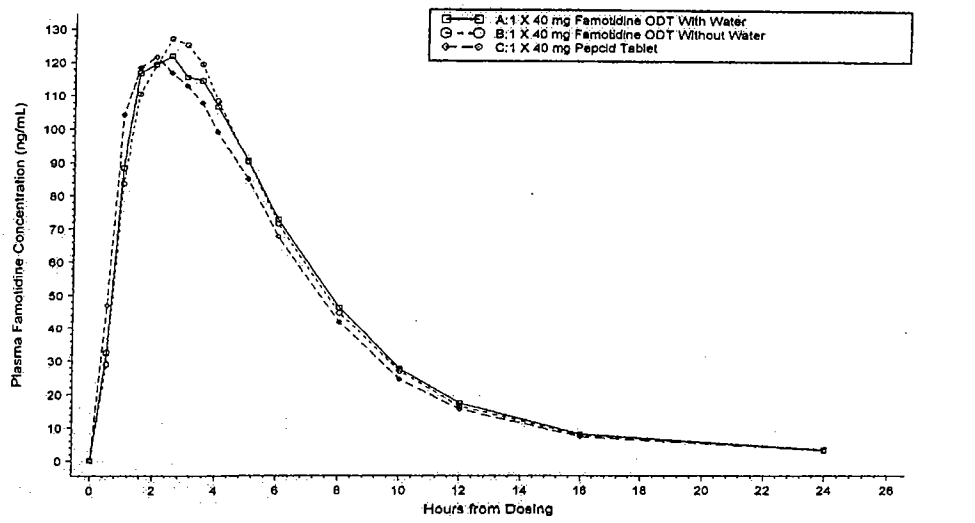
NDA 21-712 for Fluxid™ (Famotidine ODT) BE Assessment					
PK Parameters Mean (SD)	**Treatment A**	**Treatment B (Test of interest)**	**Treatment C (Reference)**	**B vs. C Point Estimate**	**90% CI**
C_{max} (ng/ml)[1]	134.6 (39.5)	135.8 (39.2)	132.1 (40.0)	-----	-----
T_{max} (hr)[1]	2.37 (0.93)	2.62 (0.89)	2.25 (1.03)	-----	-----
$T_{1/2}$ (hr)	4.89 (0.66)	4.99 (0.70)	5.16 (1.01)	-----	-----
$AUC_{0\text{-last}}$[1] (ng-hr/ml)	892.7 (207.3)	884.5 (212.3)	858.7 (231.8)	-----	-----
$AUC_{0\text{-}\infty}$[1] (ng-hr/ml)	915.3 (209.3)	906.0 (212.7)	880.9 (203.3)	-----	-----
Ln (C_{max})[2]	4.859 (0.305)	4.870 (0.294)	4.845 (0.275)	102.62	94.73-111.16
Ln ($AUC_{0\text{-last}}$)[2]	6.768 (0.236)	6.755 (0.254)	6.719 (0.274)	103.75	97.10-110.87
Ln ($AUC_{0\text{-}\infty}$)[2]	6.794 (0.234)	6.781 (0.249)	6.747 (0.269)	103.54	97.08-110.42

[1]. Arithmetic mean (± standard deviation, SD).

[2]. Log-transformed geometric least square mean (± SD).

The mean plasma profiles of three treatments are shown below in Figure 1.

Figure 1. Mean Plasma Profiles of Treatments, A, B and C.



Food effect:

The Merck's Pepcid IR tablets were originally approved under NDA 19-462 in 1986 and the effects of food on famotidine have already been established, i.e., bioavailability may be increased slightly, but is of no clinical consequence.

Since Fluxid™ ODT is to be placed on the tongue till disintegrated and then swallowed with saliva, additional dissolution process in the stomach may not be needed and therefore, sponsor's request for a waiver for the food effect study which may affect the dissolution process of ODT may be acceptable.

Lapse Time to Disintegrate on the Tongue:

For both Treatments A and B, the mean (± SD) times for Fluxid™ ODT to disintegrate on the tongue were i.e., 73.0 ± 41.1 seconds and 80.3 ± 36.6 seconds, respectively. The above mean times for Fluxid™ ODT are considered to be long. The individual data is shown below in Table 2:

Table 2. Individual Time of Disintegration (in second)

Subject	Time to Disintegration (Seconds) Treatment A	Treatment B
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		
Mean	72.97	80.30
SD	41.10	36.62
Minimum		
Median	59.00	67.00
Maximum		
N	30.00	30.00

Inspection:

Division of Scientific Investigations audit report of study SP701 is pending at the time of completion of this review. An addendum to this review discussing the implications of the audit findings will be written once the audit report is available.

Composition and Formulation:

The composition and formulation of the Fluxid™ 20 and 40 mg ODT are shown below in Table 3. The two strengths are compositionally proportional.

Table 3. The Composition and Formulation of Fluxid™ 20 and 40 mg ODT

QUANTITATIVE STATEMENTS OF COMPOSITION

Famotidine ODT, 20 mg

Ingredient Name	Role	% w/w per tablet	Quantity (mg/tablet)
Famotidine	Active		
Citric Acid, USP/EP/JP			
Colloidal Silicon Dioxide, NF/EP			
Crospovidone, NF/EP/JP			
Magnesium Stearate, NF/EP/JP			
Mannitol, USP/EP/JP			
Microcrystalline Cellulose NF/EP/JP			
Natural and Artificial Cherry Flavolope	Flavor		
Sodium Bicarbonate, USP/EP/JP			
Sucralose, NF	Sweetener		
	Total	**100.00**	**325.00**

Famotidine ODT, 40 mg

Ingredient Name	Role	% w/w per tablet	Quantity (mg/tablet)
Famotidine	Active		
Citric Acid, USP/EP/JP			
Colloidal Silicon Dioxide, NF/EP			
Crospovidone, NF/EP/JP			
Magnesium Stearate, NF/EP/JP			
Mannitol, USP/EP/JP			
Microcrystalline Cellulose			
Natural and Artificial Cherry Flavolope	Flavor		
Sodium Bicarbonate, USP/EP/JP			
Sucralose, NF	Sweetener		
	Total	**100.00**	**650.00**

Dissolution Data:

The following dissolution method was used:

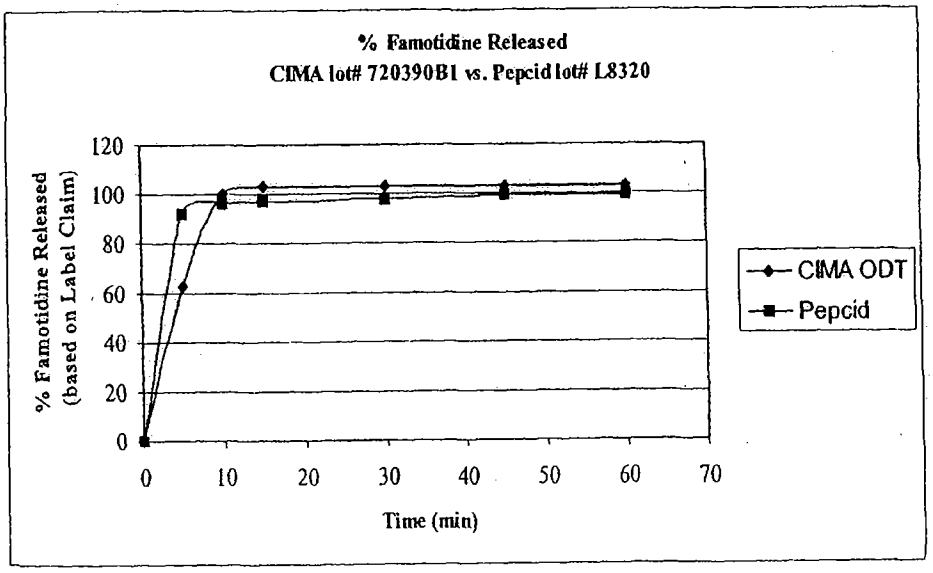
Medium: **pH 4.5, 0.1M phosphate buffer 900 mL at 37°C**
Apparatus: **USP Apparatus 2 (paddles)**
Paddle Speed: 50 rpm
Sampling at: 5, 10, 15, 30, 45, and 60 min
Specification: NLT — at 30 min

The dissolution data (n=12/lot) for the Test lot (720390B1) and Reference lot (Merck L8320) is shown in Table 4 and Figure 2 below:

Table 4. Mean Dissolution Data of The Test and Reference Lots

Time Point (min)	% Famotidine Released (based on label claim)	
	Lot 720390B1 (CIMA)	Lot L8320 (Merck)
5	63	92
10	100	96
15	103	97
30	103	98
45	103	99
60	103	99
f_2	45	

Figure 2. Mean Dissolution Profiles of The Test and Reference Lots



Since the dissolution for both lots is essentially complete in 10 minutes, indicating rapid dissolution for both products. The dissolution specifications should therefore be tightened.

Comparative dissolution data (n=12/lot) on Fluxid™ 20 mg (lot No. 720388B1) and 40 mg (Lot No. 720390B1) ODT both manufactured at CIMA Labs Inc. was also provided using three dissolution media (0.1N HCl, 0.1M Phosphate buffer pH 4.5, and 0.1M Phosphate buffer pH 6.8) to support the biowaiver for the lower strength, 20 mg ODT.

Table 5. Comparative Dissolution Data (12/lot) on Fluxid™ 20 and 40 mg ODT in Different Dissolution Media

Dissolution Mean (SD)	0.1 N HCl		pH 4.5 Phosphate Buffer		pH 6.8 Phosphate Buffer	
	20 mg	40 mg	20 mg	40 mg	20 mg	40 mg
5 min	100 (4.9)	98 (3.8)	63 (7.2)	63 (7.1)	11 (7.2)	14 (10.7)
10 min	102 (2.9)	100 (2.5)	101 (3.7)	100 (2.9)	26 (10.8)	22 (9.6)
15 min	102 (2.7)	100 (2.3)	103 (3.3)	103 (1.5)	44 (6.3)	29 (6.0)
30 min	102 (2.9)	100 (2.3)	103 (3.1)	103 (1.5)	71 (8.2)	45 (4.6)
45 min	102 (2.8)	101 (2.4)	104 (3.0)	103 (1.7)	85 (7.5)	57 (5.6)
60 min	102 (2.9)	100 (2.5)	103 (2.7)	103 (1.3)	92 (6.2)	66 (5.2)
f2	84		97		35	

The above dissolution data showed that 20 and 40 mg ODT are similar in pH 1 and 4.5 media (similarity factor f2 values being 84 and 97, respectively) and pH 6.8 phosphate medium may not be appropriate for dissolution testing. Since the 20 and 40 mg ODT are compositionally proportional and have demonstrated similar dissolution characteristics, the biowaiver for the lower strength of 20 mg ODT can be granted.

F. Analytical Section: The assay method was adequately validated

Blood samples (7 mL each) were separated by centrifugation and EDTA plasma samples were frozen at -20°C, transported to, and remained frozen until analyzed at bioanalytical site

Method: A validated LC/MS/MS method
Standard Curve:
Precision:
Accuracy:
LOQ:

QC Validation:
Precision:
Accuracy:

QC Inter-batch Variation:
Precision:
Accuracy:

QC Intra-batch Variation:
Precision:
Accuracy:

1 Page(s) Withheld

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

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

VI. Appendices

1. Proposed Package Insert (Original and Annotated, 07/03 Version)
2. Study Synopsis (No. SP701)
3. Cover Sheet and OCPB Filing/Review Form

NDA 21-712 for Fluxid™ (Famotidine) 40 and 20 mg Orally Disintegrating Tablets

Appendix 1

Sponsor's Proposed Labeling (07/03 Version)

16 Page(s) Withheld

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

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

NDA 21-712 for Fluxid (Famotidine) 40 and 20 mg Orally Disintegrating Tablets

Appendix 2

Synopsis of PK Study No. SP701

Schwarz Pharma, Inc.
Famotidine, Protocol SP701
— Project AA00277
Draft Report Date: 07 April 2003
Final Report Date: 06 May 2003
Revised Final Report Date: 19 May 2003

SYNOPSIS

TITLE:	A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT), of Famotidine 40 mg, Administered With and Without Water, Compared to a Marketed Famotidine 40 mg Tablet Formulation (Reference), Pepcid®, by Merck
SPONSOR:	Schwarz Pharma, Inc. Mequon, WI 53092
STUDY SITE:	/ /
INVESTIGATOR:	—
OBJECTIVE:	The objective of this study was to evaluate the single dose bioequivalence of the test product, a 40 mg famotidine ODT formulation, administered with and without water, compared with the reference product, Pepcid® (40 mg famotidine tablet) (Merck), when administered with water following a single 40 mg dose in the fasted state.
STUDY DESIGN:	This study had a randomized, single-dose, open-label, 3-treatment, crossover design.
STUDY PHASE:	Phase I
NUMBER OF SUBJECTS:	A total of 30 subjects, 18 males and 12 females, were enrolled in the study, and 28 subjects, 18 males and 10 females, completed the study.

TREATMENTS:

A, B: Famotidine 40 mg ODT tablets
Manufactured by CIMA LABS, INC.
Lot No.: 720390B1
Manufactured date: Dec 2002

Subjects randomized to Treatment A received a single oral dose of one 40 mg famotidine ODT tablet placed on the subject's tongue until disintegrated. The subject then was instructed to swallow the study drug mixture and was administered 240 mL of water.

Subjects randomized to Treatment B received a single oral dose of one 40 mg famotidine ODT tablet placed on the subject's tongue until disintegrated. The subject then was instructed to swallow the study drug mixture with no water administered.

C: Pepcid® (famotidine) 40 mg tablets
Manufactured by Merck and Company, Inc.
Lot No.: L8320
Expiration date: Jul 2003

Subjects randomized to Treatment C received a single oral dose of one 40 mg Pepcid® tablet taken with 240 mL of water.

PK MEASURES AND METHODS:

The pharmacokinetics of famotidine were assessed by measuring serial plasma concentrations following administration of 40 mg famotidine as the test ODT formulation administered either with water (Treatment A) or without water (Treatment B), and as the reference product, Pepcid® (Treatment C).

The pharmacokinetic parameters Cmax, Tmax, AUC(0-t), AUC(0-inf), AUCR [ratio of AUC(0-t) to AUC(0-inf)], Kel, and T1/2 were calculated using noncompartmental methods. A parametric (normal-theory) general linear model was applied to the logarithmic transformations of the Cmax, AUC(0-t), and AUC(0-inf) values. The 90% confidence intervals (CI) of the ratios

of the treatment geometric least squares (LS) means (each test/reference) were determined, and bioequivalence of each test formulation was assessed based on these 90% CI falling within the range of 80% to 125%.

RESULTS: The arithmetic means and standard deviations of plasma famotidine pharmacokinetic parameters and statistical comparisons of ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments A and C are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Famotidine for Treatments A and C

	Plasma Famotidine					
	Treatment A		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax(ng/mL)	134.581	39.487	132.063	39.974	. - .	.
Tmax(hr)	2.37	0.929	2.25	1.03	. - .	.
AUC(0-t) (ng*hr/mL)	892.72	207.31	858.23	231.81	. - .	.
AUC(0-inf) (ng*hr/mL)	915.30	209.33	880.87	233.32	. - .	.
T1/2(hr)	4.89	0.660	5.16	1.01	. - .	.
Kel(1/hr)	0.144	0.0187	0.139	0.0253	. - .	.
AUCR	0.975	0.00899	0.973	0.0123	. - .	.
ln(Cmax)	4.859	0.3054	4.845	0.2750	93.61-109.85	101.4
ln[AUC(0-t)]	6.768	0.2359	6.719	0.2736	98.05-111.94	104.8
ln[AUC(0-inf)]	6.794	0.2340	6.747	0.2687	98.08-111.55	104.6

Treatment A = 1 X 40 mg Famotidine ODT With Water: test
Treatment C = 1 X 40 mg Pepcid Tablet: reference

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The arithmetic means and standard deviations of plasma famotidine pharmacokinetic parameters and statistical comparisons of ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments B and C are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Famotidine for Treatments B and C

	Plasma Famotidine					
	Treatment B		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax(ng/mL)	135.815	39.249	132.063	39.974	. - .	.
Tmax(hr)	2.62	0.890	2.25	1.03	. - .	.
AUC(0-t) (ng*hr/mL)	884.48	212.28	858.23	231.81	. - .	.
AUC(0-inf) (ng*hr/mL)	905.98	212.70	880.87	233.32	. - .	.
T1/2(hr)	4.99	0.704	5.16	1.01	. - .	.
Kel(1/hr)	0.142	0.0208	0.139	0.0253	. - .	.
AUCR	0.975	0.00892	0.973	0.0123	. - .	.
ln(Cmax)	4.870	0.2940	4.845	0.2750	94.73-111.16	102.6
ln[AUC(0-t)]	6.755	0.2544	6.719	0.2736	97.10-110.86	103.8
ln[AUC(0-inf)]	6.781	0.2489	6.747	0.2687	97.09-110.42	103.5

Treatment B = 1 X 40 mg Famotidine ODT Without Water: test
Treatment C = 1 X 40 mg Pepcid Tablet: reference

CONCLUSION: Pharmacokinetic and statistical analyses of the data resulting from the administration of a single 40 mg famotidine dose, administered as the test ODT tablet either with or without water, and as the reference tablet (Pepcid®), have shown that under both administration conditions (with and without water) the test treatment has met the requirements for bioequivalence with the reference treatment. The 90% confidence intervals for the comparison of ln-transformed Cmax, AUC(0-t), and AUC(0-inf) were all within the acceptable range of 80% to 125% required for the conclusion of bioequivalence for famotidine, indicating that the ODT tablet formulation results in similar rate and extent of famotidine exposure compared to the reference Pepcid® tablet formulation.

NDA 21-712 for Fluxid (Famotidine) 40 and 20 mg Orally Disintegrating Tablets

Appendix 3

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-712	Brand Name	Fluxid
OCPB Division (I, II, III)	DPE II	Generic Name	Famotidine
Medical Division	GI and Coagulation	Drug Class	Histamine H_2-receptor Antagonist
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	GI disorders
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Orally disintegrating tablet
		Dosing Regimen	QD at bedtime or BID
Date of Submission	11/24/03, 02/16/04	Route of Administration	
Estimated Due Date of OCPB Review	08/20/04	Sponsor	Schwarz Pharma
Medical Division Due Date	09/02/04	Priority Classification	3 S
PDUFA Due Date	09/24/04		

Clin. Pharm. and Biopharm. Information

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

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1	1	

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 ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is Fluxid orally disintegrating tablet bioequivalent to Merck's Pepcid (famotidine) immediately release tablet?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**01/23/04**	
Secondary reviewer Signature and Date	**01/23/04**	

CC: NDA 21-712, HFD-850 (Electronic Entry or Lee), HFD-180 (B. Scroggs), HFD-870 (S. Doddapaneni, H. Malinowski, J. Hunt)

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
7/13/04 01:07:18 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/13/04 05:45:51 PM
BIOPHARMACEUTICS