

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020752**

**MEDICAL REVIEW(S)**

*J. Hendt*

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS  
MEDICAL OFFICER'S REVIEW

NDA: 20-752  
Sponsor: Merck Research Laboratories  
Drug name: Pepcid RPD™ 20mg and 40mg Wafers (famotidine)  
Date submitted: August 1, 1996  
Date received: August 5, 1996  
Review completed: March 17, 1997  
Reviewer: Kathy M. Robie-Suh, M.D., Ph.D.

MAR 21 1997

In this application the sponsor proposes a new formulation of Pepcid (famotidine) consisting of a wafer containing 20mg or 40mg of famotidine that dissolves/disintegrates when placed on the tongue. This formulation is designed to accommodate patients who desire a convenient alternative dosage form to the tablet and suspension formulations. Clinical efficacy is claimed based on studies to show bioequivalence of the wafer to the approved famotidine tablets.

**Background:**

Famotidine is a histamine H<sub>2</sub>-receptor antagonist approved for short-term treatment of duodenal ulcer (40 mg h.s.; 20mg b.i.d.), maintenance treatment of duodenal ulcer patients (20mg h.s.), short-term treatment of active benign gastric ulcer (40mg h.s.), treatment of pathological hypersecretory conditions (doses up to 640mg daily), and an intravenous formulation is available for use in patients who are unable to take medication orally. Pepcid Tablet formulation was approved for U.S. marketing on October 15, 1986 and Pepcid Oral Suspension was approved on February 2, 1987. Current labeling for the oral Pepcid formulations is attached to this review as Appendix A.

**Materials Reviewed:**

This submission consists of 17 volumes with contents as follows:

- Vol. 1.1 - Index; Synopsis of application, including annotated labeling, and benefit/risk assessment
- Vols. 1.2 through 1.5 - Chemical and Pharmaceutical Manufacturing and Control Documentation; Samples, Methods Validation and Labeling
- Vol. 1.6 - Human Pharmacokinetics and Bioavailability
- Vols. 1.7 through 1.11 - Clinical Documentation (summary of clinical pharmacology, bioavailability, efficacy and safety)
- Vols. 1.12 through 1.15 - Statistical Documentation
- Vol. 1.16 - Data Tabulations
- Vol. 1.17 - Case Report Forms

Material in volumes 1.1, 1.6 through 1.11, and 1.16 through 1.17 has been examined for this review. Three clinical studies are submitted: a taste preference test (Study O41); a

bioequivalence study (Study 042); and a multiple dose tolerability study of the famotidine wafer formulation (Study 043). These studies are briefly presented and discussed below.

**Chemistry:**

Famotidine 20mg and 40mg wafers are solid, oral dosage formulations which disintegrate when placed on the tongue. [Note: During development sponsor calls this dosage form "ZYDIS wafers"].

Chemical composition of the product to be marketed is shown in the table below:

**Market Composition**

Ingredient	mg/wafer	
Famotidine		
Gelatin		
Mannitol		
Xanthan gum		
Aspartame		
Mint Flavor		
Red Ferric Oxide		
Total Wafer Weight		

Formulations used in the bioequivalence studies were identical to the formulation to be marketed except that the famotidine 40mg wafer had red ferric oxide per wafer. The placebo formulations used in the bioequivalence studies were identical to the famotidine formulations except

Famotidine 20mg and 40mg tablets were identical in composition to the marketed famotidine tablets.

**Human Pharmacokinetic and Bioavailability Studies:**

NDA 19-462 for Pepcid tablets is referenced for information about the pharmacokinetic properties of famotidine. Briefly, about of a dose of orally administered famotidine (20-40mg) is absorbed. Elimination is primarily by the renal route as unchanged famotidine. Half-life is about 2.8 hours in healthy young subjects and 4 hours in the elderly. Half-life is prolonged in patients having severe renal impairment. (See Pepcid labeling).

Study 042 is a bioequivalence study of famotidine 40mg wafers as compared to famotidine 40mg tablets. This study is being reviewed by FDA Clinical Pharmacology and Biopharmaceutics Division. The study plan and sponsor's results are summarized briefly here.

- I. **Protocol #042:** A Single-Dose, Open, 2-Period, Crossover, Bioequivalence Study of Famotidine Film-Coated Tablets 40mg and Famotidine ZYDIS Wafers 40mg (NDA Vols. 1.7, pp. C-227 through C-390 and NDA Vol. 1.8, pp. D-1000 through D-1194).

This study was done during March, 1992. The Principal Investigator was Thorir D. Bjornsson, M.D., Ph.D., Jefferson Medical College of Thomas Jefferson University, Department of Medicine, Division of Clinical Pharmacology, 1100 Walnut Street, Suite 601, Philadelphia, Pennsylvania 19107. The study protocol and the sponsor's results are summarized and presented below.

- A. Study Plan: This was an open-label, 2-period, randomized, crossover study done in 18 healthy male subjects comparing the bioavailability of a single dose of one famotidine 40mg film-coated tablet with that of a single dose of one famotidine 40mg ZYDIS wafer. (The ZYDIS wafer

Subjects were normal healthy male non-smokers aged \_\_\_\_\_ and weighing with  $\pm 20\%$  of ideal body weight. Criteria for exclusion were use of prescription or non-prescription drugs on a regular basis or history of drug or alcohol abuse, history of renal or liver disease, any other major medical disorders, history of multiple or severe drug or food allergies, history of psychiatric disorders, use of more than 6 cups of coffee daily, unconventional or extreme dietary habits, blood donation or clinical trial participation in the prior 30 days, history of any illness or condition which might confound the study results or pose additional hazard to the subject, history of viral or gastrointestinal disease or surgery within 14 days of dosing, allergy or intolerance to H<sub>2</sub>-receptor antagonists or any other component of the study drugs, atopic condition, or subject in circumstances which might interfere with optimal participation in the study. Physical examination and medical history were done. Qualified subjects were randomly assigned to treatment sequence. For drug administration, subjects were instructed to allow the famotidine 40mg wafer to dissolve on the tongue and then swallow the saliva containing the drug. The famotidine 40mg \_\_\_\_\_ tablet was taken with 120ml of water. Washout period between treatments was 6 days. Subjects were not allowed water for 1.5 hrs after dosing. The following table shows the schedule of procedures and assessments done during the course of the study:

Study 042: Schedule of Study Procedures

	Time During Each Treatment Period (minutes)			
	Pre-Study	0	10	Post-Study
Physical examination	X			X <sup>a</sup>
12-Lead ECG	X			X <sup>a</sup>
Blood and urine for laboratory safety test*	X			X <sup>a</sup>
Drug Administration		X		
Taste Assessment			X	
Blood samples for drug assay**		X		

\* 25 ml of blood pre-study and 15ml post last treatment period. Clinical laboratory tests included hemoglobin, hematocrit, RBC, WBC with differential, platelet estimate, SGOT, SGPT, Serum alkaline phosphatase, serum total bilirubin, serum creatinine, fasting blood sugar, uric acid, serum sodium and potassium, urinalysis with microscopic.

\*\* blood samples were drawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 36 hours for drug assay; 10ml of heparinized blood taken at each time;

<sup>a</sup> Thirty-six hours following the last treatment period

<sup>b</sup> following famotidine wafers only

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sponsor's table modified, NDA Vol. 1.7, p. C-243

Adverse events were recorded including severity, seriousness, outcome, intervention and relationship to study drug.

- B. **Results: Enrollment, Demographics, and Disposition of Subjects:** Eighteen subjects were enrolled in the study. The mean age was 25.7 years (median, 24.5 yrs). Seventeen subjects were Caucasian, 1 was Black. All 18 subjects completed the study.

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**Pharmacokinetics:** Pharmacokinetic parameters for the two formulations are summarized in the following table. [Note: For some reason the values for  $C_{max}$  and  $T_{1/2}$  in the sponsor's Table 4 in the study report (p. C-251) differ a bit from those in the firm's Bioanalytical/Biopharmaceutic Report (p. C-273). Values in the following table are from the firm's Bioanalytical/Biopharmaceutic Report with the study report values in parentheses.

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Study 042: Pharmacokinetic Comparison of Famotidine Wafer with Famotidine Film-Coated Tablets

Parameter		Famotidine Wafer 40mg (A) (n= 18)	Famotidine Film- coated Tablet(B) (n= 18)	Ratio A/B (n= 18)		
				mean	90%CI	p-value
AUC (ng*hr/mL)	mean median range	1134.7 (1096.43) 1067.0	1079.8 (1049.33) 1036.7	1.04 1.00	0.95-1.06	0.4022
C <sub>max</sub> (ng/mL)	mean median range	169 (161.1) 153.2	177 (168.1) 145.7	0.96	0.85-1.08	0.5527
T <sub>max</sub> (hr)	mean median range	3.0 (3.03) 3.0	2.1 (2.08) 2.0	0.94	0.49-1.40	0.0023

<sup>1</sup> Values reported for t<sub>max</sub> (min) are the median and ranges for Treatment arms A, B, and the Ratio A/B.  
 CV = Coefficient of Variation (Standard Deviation/Mean\*100)  
 Mean Values are Geometric Least-Square Mean for AUC and C<sub>max</sub> and arithmetic mean for T<sub>max</sub>

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from sponsor's tables, NDA Vol. 1.7, p. C-251, C-273, and C-274

The sponsor estimated the sample size of 18 subjects should have 80% power to detect a difference of 14% in AUC and 13% in C<sub>max</sub> between the two treatments at an alpha level of 0.05 using a 2-tailed test. Geometric mean ratios would fall between 0.874 and 1.143 for AUC and between 0.882 and 1.133 for C<sub>max</sub>. There was 99% power that the 90% confidence intervals for the mean ratios of AUC and C<sub>max</sub> would lie within the bioequivalence interval of 0.8 and 1.25. Comparisons between treatment groups were made using ANOVA. By these criteria, the famotidine 40mg wafer formulation was bioequivalent to the film-coated tablet formulation for AUC and C<sub>max</sub>.

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The T<sub>max</sub> was greater for the wafer formulation (3.0hrs) than for the film-coated tablet formulation (2.1hrs)(p=0.0023). The sponsor's figure showing mean plasma concentrations of the two tablets over the duration of the study is attached to this review as Appendix B. Presumably the slower rise in plasma levels of famotidine with the wafer formulation is because though the wafer dissolves in the mouth, its absorption still occurs only after swallowing and not through the oral mucosa.

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*Taste Assessment:* Six subjects characterized the taste/aftertaste of the wafer as "better than average for a medication", 9 as "average for a medication" and 3 as "worse than average for a medication".

*Safety:* One subject experienced an adverse event during the study. This was subject #001 who had 5 hrs of mild headache after the famotidine 40mg tablet dose. This event was not serious and was judged probably not related to study medication.

- C. Reviewer's Comments: By the sponsor's analyses, the famotidine 40mg wafer formulation and the 40mg tablet formulation were bioequivalent with respect to AUC and  $C_{max}$ . The  $T_{max}$  for the wafer formulation was significantly longer than for the tablet (3.0 hrs as compared to 2.1 hrs). It is not clear to me why this is the case. Nevertheless, because the efficacy of prescription famotidine for approved indications is apparent only after multiple dosing for weeks to months, the difference in  $T_{max}$  is not likely to be of clinical significance.

Both the wafer formulation and the tablet formulation were well-tolerated by the subjects in this study.

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**Other Clinical Studies:**

- I. **Protocol #041: Famotidine New Flavor Taste Test: A Single-blind Taste Test to Evaluate Three Flavors of ZYDIS Tablets Containing 40mg of Famotidine (NDA Vol. 1.9, pp. D-1204 through D-1581)**

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- A. Study Plan: Study 041 was a taste test evaluating preference among 3 flavors of the famotidine 40mg wafer product. The study was performed at 4 sites in the U.S. (David Kogut, M.D., Statesville, NC; Benjamin Levy, M.D./Raoul Hansen, M.D., Hartford, CT; Lawrence Wruble, M.D., Memphis, TN; Martin Collen, M.D./Michael Solinger, M.D., Loma Linda, CA). The aims of the study were to determine the marketability of the wafer formulation and to determine which of 3 flavors (peppermint, mint or peppermint-banana) was preferred by consumers. Subjects were males or females aged 21 years or older with at least half of the subjects being aged 60 yrs or older. They must have used antacids within the prior 3 months for upper gastrointestinal disorders. Criteria for exclusion were: pregnancy or lack of adequate birth control; lactation; history of serious medical illness (including gastrointestinal illness and/or surgery; current users of prescription antisecretory products or antacids prescribed by a physician; use of  $H_2$ -receptor antagonist, misoprostol, omeprazole, systemic corticosteroids, anticholinergics, metoclopramide, anticoagulants, or antineoplastics within 1 week prior to study; use of lower gastrointestinal medications within the past 24 hrs; use of antacids solely for diarrhea or as a calcium supplement; recent history of substance abuse; participation in any experimental study within past 30 days; prior adverse reaction to famotidine; conditions which might interfere with the data interpretation or create undue risk. Subjects were recruited and preliminarily screened by telephone by calls to random households in the area of the study site. Following preliminary screening qualified subjects were invited to come to the study site at an appointed time to taste a medication used to reduce stomach acid and told they would be given \$20 for doing the test. At the taste test each subject was given a 40mg tablet to taste and swallow. The subject graded the taste on a scale of 0 to 10 and then answered specific questions about the taste of the product. After 30 minutes the taste test was repeated using a second (different) flavored

famotidine 40mg product to taste. All study medications were identical in appearance and were given in six different treatment sequences, balanced to facilitate analysis. Each taste test was preceded by the subject eating a salted cracker and sipping a cup of water. Subjects finally were asked to compare the tastes of the two products. All subjects gave written informed consent for study participation. There were no clinical laboratory evaluations in this study.

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B. Results: This study was conducted from December, 1991 through January, 1992. Study duration was 18 days. A total of 450 subjects received study medication. Of the study population 51% were female and 49.3% were aged 60 years or older. Enrollment was about equally distributed among the four sites. All subjects completed the study. There were 7 clinical adverse experiences all mild to moderate in severity reported during the study. Two adverse events were judged to be probably drug related. These were: mild nausea lasting 5 minutes in a 37 year old woman and an erythematous, macular, pruritic rash on the abdomen lasting 18 days in a 50 year old man with a history of allergies to penicillin and tetracycline. One subject experiencing an adverse event (rhinorrhea) was 72 yrs old and one subject discussed above was 50 yrs. The other subjects experiencing adverse events were in their 30s. Other events reported were dizziness, abdominal distension, sinus disorder and abdominal pain.

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C. Reviewer's Comments: The doses of study medication given in this study generally were well-tolerated. There did not appear to be any relationship between adverse events and age or gender. The events felt probably related to study medication (rash and nausea) are already listed in the prescription labeling for famotidine.

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II. **Protocol #043: Multiple-dose Tolerability Study of the Zydys Formulation of Famotidine (NDA Vol. 1.10 p. D-1582 through Vol. 1.11, p. D-2274)**

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This was a European, multicenter, randomized, double-blind, placebo-controlled, parallel group safety study of the famotidine 20mg and 40mg wafer done from 4/92 to 7/92. No efficacy assessments were made.

Principal Investigators were:

Dr. M. Seiberling  
Biodesign CRF Institute  
for Clinical Pharmacology  
Freiburg, Germany

Dr. A. Mallat  
Hospital Henri Mondor  
Creteil, France

Dr. R. Sennewald  
L.A.B. GmbH and Co.  
Neu-Ulm, Germany

Dr. G. Strauch  
Hospital Cochin  
Paris, France

Dr. J. Bergmann  
Hospital Lariboisiere  
Paris, France

Dr. G. Dobrilla  
Regional Hospital of Bolzano  
Rome, Italy

The study protocol is summarized briefly below.

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- A. Study Plan: This was a randomized, double-blind, placebo-controlled study designed to compare the tolerability of famotidine 20mg b.i.d. and 40mg b.i.d. given for 14 days to that of placebo. Subjects were to be 180 normal adults aged Females were to be sterile or postmenopausal. Criteria for exclusion were: medical condition requiring continuous concurrent medication; history of illness that may interfere with interpretation of the study results or pose additional risk to the patient; history of a clinically significant oropharyngeal disease or condition; history of a malignant disorder (other than minor dermatologic malignancy); history of unstable cardiovascular, renal or hepatic disease; clinically significant abnormality on screening laboratory studies; history of drug abuse or recreational drug use (past or current); alcohol abuse; significant drug allergies; consumption of >6 cups of caffeinated coffee daily; regular use of any medication (including over-the-counter medicines) which might interfere with the study; any situation or condition which might interfere with study participation. All subjects gave informed consent for study participation. Prestudy screening consisted of medical history, physical examination, and clinical laboratory studies. Qualified subjects were randomized to either placebo, famotidine 20mg b.i.d., or 40mg b.i.d. Because the famotidine 40mg and 20mg tablets were different in appearance, a double-dummy technique was used; so each patient took 2 tablets for each dose. Subjects were to return for 2 follow-up visits - at 7 days and at 14 days (final visit). Adverse experiences were elicited by asking patients "How do you feel?" The first drug dose was to be administered at the study site and subjects were to remain for 30 minutes after which they were asked about adverse events ("How do you feel?") and asked about the drug taste. Adverse events were to be Subjects also were to grade the taste/aftertaste of the test medication. At final visit physical examination and clinical laboratory tests were repeated and adverse events recorded. For purposes of analysis the sponsor calculates that the study should be able to detect a difference in adverse event rates of 25% with 80% power at the 0.05 level of significance (2-tailed), assuming an event rate of Adverse event data were to be analyzed Clinical laboratory studies included hemoglobin, hematocrit, WBC with differential, platelet count, SGOT, SGPT, alkaline phosphatase, total bilirubin, creatinine, BUN, and urinalysis. Concurrent medications and alcohol use were prohibited during the study. Compliance with study medication was assessed by pill counts.

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The data were initially recorded in work booklets/worksheets and then typed onto the Case Report Forms.

- B. Results: A total of 192 subjects were enrolled into this study. Sixty subjects were from Seiberling's site, 51 from Dobrilla's site, 21 from Sennewald's site and 20 from each of the other sites. There were 64

subjects in each treatment group and subjects were evenly distributed among the treatments at each site. All subjects completed the study. Demographic characteristics of the subjects are summarized in the following table:

**Study 043: Demographic Features of Study Population**

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	Placebo (n = 64)	Famotidine 20mg b.i.d. (n = 64)	Famotidine 40mg b.i.d. (n = 64)	Total (n = 192)
Gender				
male	67%	67%	61%	65.1%
female	33%	33%	39%	34.9%
Age				
mean	32.9	32.6	33.8	33.1
median	29	29	31	30
range				
Race				
White	98%	100%	97%	98.4%
Black	2%	0%	3%	1.6%

reviewer's original table, based on information in sponsor's tables, NDA Vol. 1.10, pp. D-1597 and D-1598

The treatment groups were generally well-matched for demographic characteristics; however, there was a About 90% of subjects had some history of caffeine use; about 14% of patients used some medication during the treatment period; almost all of this use was of hormones and synthetic substitutes.

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Adverse experiences elicited by asking the question, "How are you doing?" were reported by 35 subjects (9 placebo, 11 famotidine 20mg, 15 famotidine 40mg). All the adverse events reported are summarized in the following table:

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Study 043: Table of All Clinical Adverse Experiences

Adverse Event	Placebo	Famotidine 20mg	Famotidine 40mg
Asthenia/Fatigue	2 (3.1%)	2 (3.1%)	2 (3.1%)
Pain, Abdominal	0	2 (3.1%)	3 (4.7%)
Diarrhea	1 (1.6%)	3 (4.7%)	3 (4.7%)
Flatulence	3 (4.7%)	1 (1.6%)	0
Nausea	1 (1.6%)	1 (1.6%)	2 (3.1%)
Headache	1 (1.6%)	0	3 (4.7%)
Herpes infection	---	---	1 (1.6%)
Chest pain	---	---	1 (1.6%)
Angina pectoris	---	1 (1.6%)	---
Premature ventricular contraction	---	1 (1.6%)	---
Constipation	1 (1.6%) 1 1	1 (1.6%)	---
Dry mouth	(1.6%)	1 (1.6%)	---
Eructation	---	---	1 (1.6%)
Calcaneus fracture	---	---	1 (1.6%)
Paresthesia	---	1 (1.6%)	---
Somnolence	---	---	1 (1.6%)
Upper respiratory infection	---	---	1 (1.6%)
Pharyngitis	---	---	1 (1.6%)
Rhinitis	---	1 (1.6%)	1(1.6%)
Conjunctivitis	---	1 (1.6%)	---
Cervical root syndrome	1 (1.6%)	---	---
Migraine	1 (1.6%)	---	---
Vertigo	1 (1.6%)	---	---

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reviewer's original table based on information in sponsor's tables, NDA Vol. 1.10, pp.D-1600, D-1667 and D-1668.

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No events were judged to be serious. Only two events (calcaneal fracture in a famotidine 40mg patient and cervical root syndrome in a placebo patient) were graded severe in intensity. Most events (about 78%) were mild in intensity. Events judged to be probably study drug related included dry mouth in a famotidine 20mg patient who also had constipation, asthenia/fatigue in a famotidine 20mg patient who also had diarrhea, asthenia/fatigue in a famotidine 40mg patient, and asthenia/fatigue in a placebo patient who also had diarrhea and flatulence. Events in the famotidine groups judged to be possibly study drug related included constipation, asthenia/fatigue, flatulence, diarrhea, eructation, headache, chest pain, and somnolence. A 27 year old man with no significant past medical history noted, no medications and normal physical exam was noted to have premature ventricular contractions one day after discontinuing study medication. No action was taken for any of the events in this study.

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There were no deaths and no patients discontinued study prematurely due to adverse events. There were no significant changes vital signs during study treatment.

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A few abnormal laboratory values found on end of study clinical laboratory studies were reported as adverse events. These are listed in the following table. Except where noted below, events were judged to be definitely not study drug related. No interventions were made.

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**Study 043: Laboratory Values Reported as Adverse Events**

Event	Pt #	Treatment	Comments
Proteinuria	38	placebo	30 yo man
Decreased neutrophils and increased lymphocytes	63	placebo	39 yo man; event probably not study drug related
Increased AST and increased ALT	65	placebo	26 yo man; AST sl elevated at study entry; essentially unchanged; ALT normal at entry, slightly elevated at completion; judged possibly study drug related
Pyuria	71	fam 20mg	37 yo woman; definitely not drug related
Increased eosinophils	143	fam 20mg	Mild elevation in a 28 yo man; judged possibly study drug related
Pyuria	149	fam 20mg	24 yo man; retested 2 days later, result normal
Pyruia	125	fam 20mg	29 yo woman
Decreased neutrophils and increased lymphocytes	68	fam 40mg	25 yo man
Epithelial cells in urine	144	placebo	45 yo woman; retested 4 days later, result normal
Proteinuria and pyuria	110	fam 40mg	23 yo man
Proteinuria and hematuria	119	fam40mg	31 yo woman; many epithelial cells in urine at screening; elevated WBC and RBC in urine at study completion

reviewer's original table, based on information in sponsor's table, NDA Vol. 1.10, p. D-1795 through Vol. 1.11, p. D-2245 and sponsor's table NDA Vol. 1.10, p. D-1602

For the most part laboratory values showed no significant changes from the beginning to the end of the study. Hematocrits of 7 placebo subjects, 2 famotidine 20mg subjects, and 2 famotidine 40mg subjects showed a decrease of at least 6%. BUN increased by at least 25% in 7 placebo subjects, 6 famotidine 20mg subjects, and 9 famotidine 40mg subjects. Bilirubin increase by 0.6mg/dl or more in 3 placebo subjects, 2 famotidine subjects, and 1 famotidine 40mg subject. AST (SGOT) increased by 75% or more in 3 placebo subjects, 0 famotidine 20mg subjects, and 2 famotidine 40mg subjects. ALT (SGPT) increased by 75% or more in 5 placebo subjects, 3 famotidine 20mg subjects and 3 famotidine 40mg subjects.

Significantly more placebo and famotidine 20mg subjects had increases of at least 5% in neutrophils counts as compared to famotidine 40mg subjects (14

subjects, 11 subjects, and 3 subjects, respectively). Serum creatinine rose slightly in the famotidine 20mg group and the famotidine 40mg group (0.02 mg/dl and 0.02 mg/dl) and decreased slightly in the placebo group (-0.03mg/dl); this difference between the famotidine groups and placebo was statistically significant. There were no other significant differences among the treatment groups with regard to changes in laboratory values during the study. In all treatment groups alkaline phosphatase showed a statistically significant decrease during the study ( $p < 0.05$ ).

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- C. Reviewer's Comments: There were no meaningful differences between the famotidine groups and placebo in incidence or type of adverse events. Simply asking the question, "How are you doing?" as was done in this study may not be the most effective way to assure thorough collection of adverse events. Nevertheless, this study generally supports the safety of short-term (2-weeks) use of famotidine 20mg b.i.d. and 40mg b.i.d. Adverse events experienced in this study were similar to the established profile of already approved Pepcid (famotidine) tablets. Famotidine wafer seems to have been well-tolerated in the normal volunteers in this study.

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**Summary of Safety Information:**

Clinical Trials: The clinical trial safety database for this application consists of 3 studies (Studies #041, #042 and #043 presented above) in which 578 subjects received famotidine wafer, 18 received famotidine tablets, and 64 received placebo. All these exposures were in normal subjects. Exposure to the famotidine wafer ranged from 1 day (single dose in taste test [Study 042] and cross-over pharmacokinetic study [Study 041]). The longest duration of exposure was 14 days in 64 subjects administered famotidine 20mg b.i.d. and 64 subjects administered famotidine 40mg b.i.d. Ninety-five percent of subjects were Caucasian, 55% were males, and mean age was 47 years (median, 44 yrs).

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There were no serious adverse events, deaths or discontinuations due to adverse events in these studies. Frequency of adverse events was similar with famotidine and placebo treatment and types of adverse events reported for these groups were generally similar. Events occurring at a frequency of  $\geq 2\%$  in either of these studies included asthenia/fatigue, headache, diarrhea and abdominal pain. Asthenia, fatigue, headache, and diarrhea are listed in the approved labeling for famotidine tablets. There were no clinically meaningful differences in abnormal clinical laboratory values between famotidine and placebo treatments in these studies. No relationship between all or particular adverse events and famotidine dose were apparent in these studies. These studies generally support the established safety profile of famotidine as reflected in the Pepcid Tablet labeling.

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Famotidine Tablets Database:

In support of the safety of prescription famotidine tablets, the sponsor has submitted the "Safety Profile of Prescription Famotidine" section from the OTC Famotidine application (NDA 20-325, Vol. 1.15, pp. 8-B-00325 through 8-B-00486, submitted April 1, 1993). This information was reviewed in my Medical Officer's Reviews of NDA 20-325 dated Jan 12, 1994 and June 2, 1994). Prescription famotidine was found to have a good safety profile with the observed adverse events and laboratory abnormalities adequately reflected in the labeling for Pepcid. However, the database for this information was closed May 31,

1992.

Pepcid Tablet formulation was approved for U.S. marketing in October 15, 1986 and Pepcid Oral Suspension was approved on February 2, 1987. Examination of the safety information presented in the most recent Annual Report for Pepcid Tablets (NDA 19-527) submitted 4/2/96, and in the Periodic Adverse Experience Reports for Pepcid Tablets and for Pepcid Suspension (NDA 19-462) submitted after May, 1992 reveal no new adverse events that need to be included in the famotidine labeling. Counts of total and serious events appearing in the Periodic Adverse Experience Reports are summarized in the table below:

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Counts of Forms Submitted in Periodic Adverse Event Reports Since 1992

Report	Total #E Reports*	Reports of Serious Events	Initial 15-Day Reports	Increased Frequency
<b>Pepcid Tablets (NDA 19-462):</b>				
P-015, submitted 12/15/93 NDA Vol. 38.1 (covers 10/16/92- 10/15/93)	122 (5FU)	7	22	0
P-016, submitted 12/20/94 NDA Vol. 40.1 (covers 10/16/93-10/15/94)	124 (7FU)	2	33	0
P-17, submitted 12/13/95) NDA Vol. 44.1 (covers 10/16/94-10/15/95)	158 (12FU)	1	37	2 (confusion, pancytopenia)
P-018, submitted 12/13/96 NDA Vol. 48.1 (covers 10/16/95-10/15/96)	249 (12FU)	4	22	1 (liver function abnormality)
<b>Pepcid Suspension (NDA 19-527):</b>				
P-013, submitted 3/10/92 NDA Vol. 5.1 (covers 2/3/91- 2/2/92)	2 (0)	0	0	0
P-014, submitted 4/4/94 NDA Vol. 5.1 (covers 2/3/93-2/2/94)	1 (1)	0	0	0
P-015, submitted 4/2/95 NDA Vol. 6.1 (covers 2/3/94-2/2/95)	1 (0)	0	0	0
P-016, submitted 3/22/96 NDA Vol. 7.1 (covers 2/3/95-2/2/96)	6 (0)	0	1	0

\* Number of followup reports in parentheses

reviewer's original table

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Among the 10 reports submitted for the suspension formulation, 4 of the cases in the 3/22/96 submission and the one case in the 4/4/94 report were pediatric patients. These amount to half of the adverse event reports for the suspension. For the tablet formulation, on the other hand, there were only 6 pediatric cases identified among the 653 cases listed in these periodic reports. [Note: Age was not reported for some of the patients in these reports]. This information suggests that the suspension formulation is more likely to be used in pediatric patients than the tablet formulation. The wafer formulation seems to me also a formulation likely to be used in the pediatric population.

APPEARS THIS WAY

ON ORIGINAL

The current Adverse Reactions and Precautions sections of the Pepcid oral formulations labeling adequately reflect the safety profile of famotidine.

APPEARS THIS WAY

ON ORIGINAL

Foreign Marketing: Famotidine wafer is marketed in 20 countries worldwide for treatment of duodenal ulcer, gastroesophageal reflux disease and Zollinger-Ellison syndrome. It was first approved in April, 1993 in Sweden. As of June, 1996 is it marketed in Armenia, Australia, Belgium, Brazil, Denmark, Finland, France, Georgia, Germany, Holland, Iceland, Italy, Luxemburg, Mexico, New Zealand, Norway, Portugal, Russia, Sweden and Switzerland.

APPEARS THIS WAY

ON ORIGINAL

There have been 2 adverse event reports filed for the wafer formulation. In one case a 76 year old woman in Finland who had been taking famotidine 20mg wafer once daily for dyspepsia for 10 days developed desquamation of the tongue. famotidine wafer was discontinued. No further information is available. In another case also from Finland, a 45 year old woman taking famotidine wafer 20mg daily for hiatal hernia and esophagitis developed facial edema, rash and myalgia 3 days after starting famotidine. The famotidine was discontinued and symptoms resolved. This patient also was taking naproxen.

APPEARS THIS WAY

ON ORIGINAL

**Benefit/Risk Assessment:**

The sponsor has developed a wafer formulation containing 20mg or 40mg of famotidine to be used as an alternative dosage for already approved famotidine indications. This formulation would provide a convenient dosage form for patients who do not like tablets or have difficulty taking tablets. It may be particularly useful in the elderly where surveys conducted by the sponsor estimate that about 25% of patients over the age of 80 years have some difficulty with swallowing. [The sponsor estimated in 1993 that about 500,000 nursing home patients had taken an H<sub>2</sub>-receptor antagonist orally during the prior month and that of these about 150,000 have difficulty swallowing or refuse to swallow oral medication]. The wafer formulation might be anticipated to be particularly useful in this patient population.

APPEARS THIS WAY

ON ORIGINAL

The current submission has not addressed use of Pepcid wafer in pediatric patients. The current Pepcid labeling does not contain information about use of the product in pediatric patients.

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**Proposed Labeling:**

The sponsor has proposed making changes to the existing Pepcid Tablet, Pepcid Oral Suspension labeling to include the wafer formulation. The sponsor's annotated proposed labeling is attached to this review as Appendix C. The proposed changes have been reviewed and I have the following comments.

- Under the **DESCRIPTION** section and in the last paragraph of the **DOSAGE AND ADMINISTRATION** section, the sponsor describes the wafers as "rapidly dissolving". Clinical data to indicate the length of time the wafer takes to dissolve/disintegrate were not submitted. FDA Chemistry Review should address appropriateness of the proposed phrasing based on the *in vitro* dissolution studies and any other relevant information.
- Under the *Pharmacokinetics* section the sponsor indicates that: "All three oral formulations of PEPCID are rapidly absorbed..." The sponsor has not provided supporting information to justify using the term 'rapidly absorbed'. I suggest revising the proposed sentence to say:

"After oral doses of either of the three formulations, peak plasma levels occur in 1-3 hours."

**Conclusions and Recommendations:**

From a clinical perspective, I recommend approval of Pepcid 20mg Wafers and Pepcid 40mg Wafers, provided FDA concurs that bioequivalence of the wafers with already approved famotidine tablets has been established.

I agree that the wafer formulation should share labeling with the other oral formulations (tablet and suspension). The proposed labeling should be revised as indicated under Proposed Labeling above.

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ON ORIGINAL

/S/

Kathy M. Robie-Suh, M.D., Ph.D.

3/21/97

- cc:
- NDA 20-752
- HFD-180
- HFD-180/SFredd
- HFD-180/KRobie-Suh
- HFD-181/MFolkendt
- HFD-180/JChoudary

3/21/97  
/S/

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NDA 20-752

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HFD-180/EDuffy

HFD-870

HFD-710/Biometrics

f/t 3/21/97 jgw

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APPENDIX A

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NDA 20-752  
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APPENDIX B

Famotidine (MK-208) Prot. No. 042  
Dr. Bjornsson

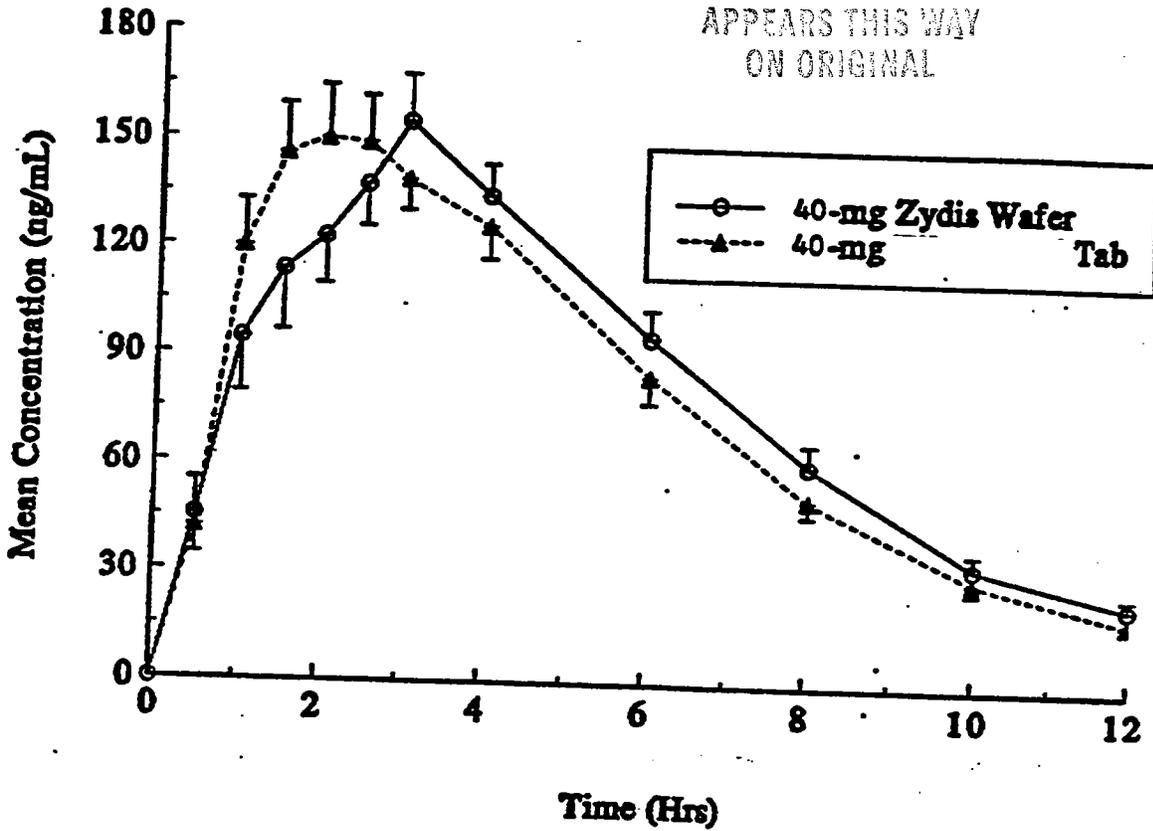
-20-

C. Pharmacokinetics (Cont.)

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FIGURE 1

MEAN (+ S.E.) PLASMA CONCENTRATIONS OF THE TWO TABLETS



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