TRADE: PEPCID

SHARP & DOHME GENERIC: FAMOTIDINE

APRVL

LTR

OCT 15 1986

NDA 19-462

Merck Sharp & Dohme Research Laboratories
Division of Merck & Co.
Attention: Gerard D. Picot, Ph.D.
West Point, PA 19486

Dear Dr. Picot:

Please refer to your June 24, 1985 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pepcid (famotidine) Tablets.

We also acknowledge receipt of your amendments dated October 3 and 7, 1986.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on October 7, 1986. Accordingly, the application is approved.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

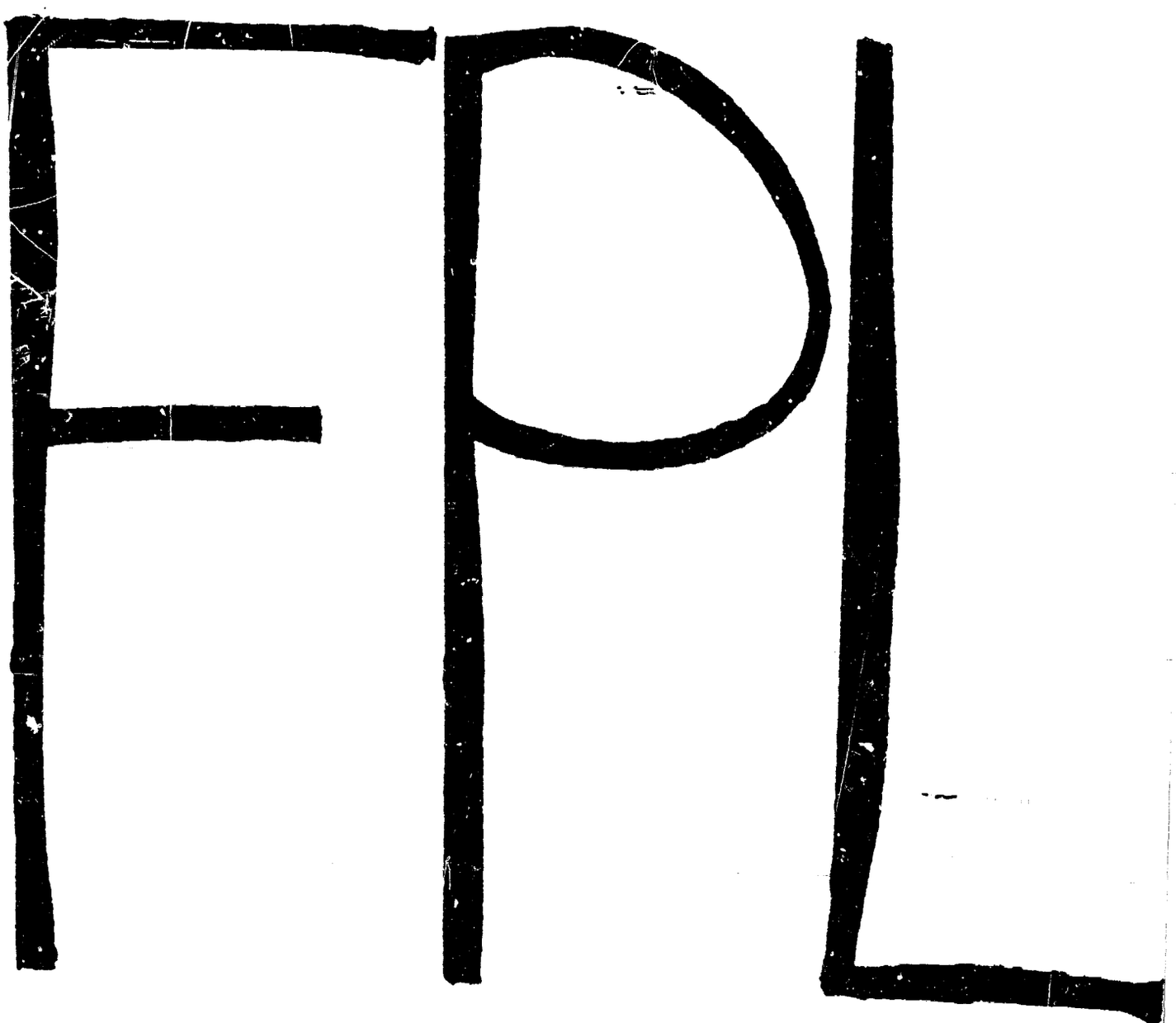
Ms. Constance Burner Henry
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-100/Dr. Temple
HFN-232 (with labeling)
HFN-110/CHenry/10/9/86;10/10/86;10/10/86
sb/10/10/86;10/10/86;10/14/86;10/14/86/4445
R/D: NMorgenstern/10/10/86
RLipicky/10/10/86;10/14/86
PDeslauriers/10/10/86
WBachrach/10/10/86
RWolters/10/10/86;10/14/86

APPROVAL

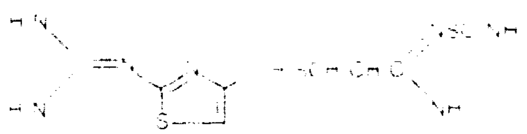


MSD | PEPCID® TABLETS (FAMOTIDINE, MSD)

PEPCID®
(Famotidine, MSD)

DESCRIPTION

The active ingredient in PEPCID® Tablets (Famotidine, MSD) is a histamine H₂-receptor antagonist. Famotidine is 3-[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-N-(aminosulfonyl)propanimidamide. The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.43. Its structural formula is:



Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, corn starch, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

GI Effects

PEPCID is a competitive inhibitor of histamine-2 receptors. The primary clinically important pharmacologic activity of PEPCID is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by PEPCID, while changes in pepsin secretion are [illegible]

[illegible] PEPCID [illegible] basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. After oral administration, 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 [illegible] 40 mg was 10 to 12 hours.

[illegible]

[illegible] gastric pH was raised by evening doses of 20 and 40 mg of PEPCID to mean values of 5.0 and 6.4, respectively. When PEPCID was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of PEPCID was raised to about 5.

PEPCID had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by PEPCID.

Other Effects

Systemic effects of PEPCID in the CNS, cardiovascular, respiratory or endocrine systems have not been found to date. Serum prolactin levels did not rise after intravenous 20 mg bolus doses of PEPCID. No antiandrogenic effects have been detected.

Pharmacokinetics

PEPCID is incompletely absorbed. The bioavailability of oral doses is 40-45%. Bioavailability may be slightly increased by food, or slightly decreased by antacids; [illegible] of no clinical consequence. PEPCID undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen to 20% of PEPCID in plasma is protein bound. PEPCID has an elimination half-life of 2.5-3.5 hours. PEPCID is eliminated by [illegible] 65-70% [illegible] minutes. Renal clearance is 250-450 mL/min, indicating some tubular excretion. [illegible] 65-70% of an intravenous [illegible] found. The only metabolite identified in man is the S-oxide.

There is a close relationship between creatinine clearance values and the elimination half-life of PEPCID. In patients with [illegible]

[illegible] see PRECAUTIONS, DOSAGE AND ADMINISTRATION.

In elderly patients, there are no clinically significant age-related [illegible] PEPCID.

[illegible]

[illegible] placebo [illegible] duodenal ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients receiving PEPCID than for patients receiving placebo; patients receiving PEPCID also took less antacid than the patients receiving placebo.

Long-Term Maintenance Treatment of Duodenal Ulcers [illegible]

PEPCID, 20 mg [illegible] was compared [illegible] as maintenance therapy [illegible] controlled multicenter studies of patients with endoscopically confirmed healed duodenal ulcers. In the U.S. study the observed ulcer incidence within 12 months in patients treated with placebo was [illegible] 2.4 times greater than in the patients treated with PEPCID. The [illegible] patients treated with PEPCID had an observed cumulative ulcer incidence of 23.4% compared to an observed ulcer incidence of 56.6% in the 89 patients receiving placebo [illegible]. These results were confirmed in an international study where the cumulative observed ulcer incidence within 12 months in the 307 patients treated with PEPCID was 35.7%, compared to an incidence of 75.5% in the 325 patients treated with placebo (p < 0.01).

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)

In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome with or without multiple endocrine adenomas, PEPCID significantly inhibited gastric acid secretion and controlled associated symptoms. Doses from 20 to 160 mg q 6 h maintained basal acid secretion below 10 mEq/hr; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. PEPCID was well tolerated at these high dose levels for prolonged periods (greater than 12 months) in eight patients, and there were no cases reported of gynecomastia, increased prolactin levels, or impotence.

INDICATIONS AND USAGE

PEPCID is indicated in:

1. *Short term treatment of active duodenal ulcer.* Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.

2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies have not extended beyond one year.

3. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas).*

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

PRECAUTIONS

General

Symptomatic response to therapy with PEPCID does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency

Longer intervals between doses or lower doses may need to be used in patients with severe renal insufficiency (creatinine clearance < 10 mL/min) to adjust for the longer elimination half-life of famotidine. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.) However, currently, no drug-related toxicity has been found with high plasma concentrations of famotidine.

Drug Interactions

No drug interactions have been identified. Studies with famotidine in man, in animal models, and in vitro have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for PEPCID.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate. In in vivo studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to [illegible] mg/kg/day, fertility and reproductive performance were not affected.

Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day, respectively, and in both species at IV doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to PEPCID. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 600 times the usual human dose. It is not known whether this drug is secreted in human milk. Because many drugs are secreted into human milk and because of the potential for serious adverse reactions in nursing infants from PEPCID, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). Dosage adjustment in the case of severe renal impairment may be necessary.

ADVERSE REACTIONS

The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In those [illegible] in which PEPCID Tablets were compared [illegible] incidence of adverse experiences [illegible] PEPCID Tablets, 45 [illegible] [illegible] placebo group.

The following adverse [illegible] or in more than 1% [illegible] controlled clinical trials [illegible] drug: headache (4.7%) [illegible] and diarrhea (1.7%).

The following other [illegible] [illegible] relationship to [illegible] established for these infrequent [illegible] cannot be excluded.

Body as a Whole: fever, asthenia [illegible]

Cardiovascular: palpitations [illegible]

Gastrointestinal: nausea, vomiting [illegible] anorexia, dry mouth, liver enzyme [illegible]

Hematologic: thrombocytopenia [illegible]

Hypersensitivity: orbital edema [illegible]

Musculoskeletal: musculoskeletal [illegible]

Nervous System/Psychiatric: [illegible] zure (single report), psychic [illegible] sion, anxiety, decreased [illegible] insomnia, somnolence.

Respiratory: bronchospasm [illegible]

Skin: alopecia, acne, pruritus [illegible]

Special Senses: tinnitus, taste [illegible]

OVERDOSAGE

There is no experience [illegible] Doses of up to 640 mg/day [illegible] pathological hypersecretory [illegible] adverse effects. In the event of overdosage [illegible] be symptomatic and supportive [illegible] should be removed from the gastro[illegible] should be monitored, and supportive [illegible] employed.

The oral LD_{50} of famotidine in male [illegible] mice was greater than 3000 mg/kg [illegible] acute oral dose in dogs exceeded 2[illegible] not produce overt effects at any dose [illegible] and dogs, but induced significant [illegible] depression in rabbits starting with [illegible] intravenous LD_{50} of famotidine [illegible] 254-563 mg/kg, and the minimum [illegible] dogs was approximately [illegible] tion in IV treated dogs were [illegible]

Issued October 1986

[illegible] been identified. Studies with [illegible] models, and *in vitro* have shown [illegible] the disposition of compounds [illegible] microsomal enzymes, e.g. [illegible]mpounds tested in man include [illegible]toin, diazepam, aminopyrine [illegible]een as an index of hepatic drug [illegible]nd no significant effects have

[illegible] *Impairment of Fertility*

[illegible] a 32 week study in mice [illegible] mg/kg/day [illegible] human dose for active duo[illegible] [illegible]dence of carcinogenic potential

[illegible] the microbial mutagen test [illegible] *typhimurium* and *Escherichia* [illegible]ver enzyme activation at con[illegible] plate. In *in vivo* studies in mice [illegible] chromosomal aberration test, [illegible]ffect was observed.

[illegible] oral doses of up to 2000 mg/kg [illegible] to 200 mg/kg/day fertility and [illegible] not affected.

[illegible] been performed in rats and [illegible] [illegible] 500 mg/kg/day respec[illegible] [illegible] of up to 200 mg/kg/day [illegible] evidence of impaired fertility [illegible] PEPCID. While no direct fetotoxic [illegible] sporadic abortions occurring [illegible] marked decreased food intake [illegible] doses of 200 mg/kg/day [illegible] higher. There are, however, [illegible] studies in pregnant women [illegible] studies are not always predic[illegible] [illegible] should be used during [illegible]

[illegible] rats have shown that fam[illegible] milk. Transient growth depres[illegible] rats suckling from mothers [illegible]oses of at least 600 times the [illegible] known whether this drug is [illegible]

[illegible] children have not been estab[illegible]

[illegible] required based on age [illegible] see [illegible] [illegible] severe renal impairment may be [illegible]

[illegible]E REACTIONS

[illegible] listed below have been reported [illegible]ational clinical trials in approx-

imately 2500 patients. In those controlled clinical trials in which PEPCID Tablets were compared to placebo, the incidence of adverse experiences in the group which received PEPCID Tablets 40 mg at bedtime, was similar to that in the placebo group.

The following adverse reactions have been reported to occur in more than [illegible] of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

The following other adverse reactions have been reported in clinical trials. While a causal relationship could not be established for these infrequently reported events, causality cannot be excluded.

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: palpitations

Gastrointestinal: nausea, vomiting, abdominal discomfort, anorexia, dry mouth, liver enzyme abnormalities

Hematologic: thrombocytopenia

Hypersensitivity: orbital edema, conjunctival injection

Musculoskeletal: musculoskeletal pain, arthralgia

Nervous System/Psychiatric: paresthesias; grand mal seizure (single report); psychic disturbances including depression, anxiety, decreased libido, hallucinations (single report); insomnia, somnolence

Respiratory: bronchospasm

Skin: alopecia, acne, pruritus, rash, dry skin, flushing

Special Senses: tinnitus, taste disorder

OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient [illegible] supportive therapy [illegible] employed.

The [illegible] LD_{50} of famotidine in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 2000 mg/kg. Famotidine did not produce overt effects at high oral doses in mice, rats, cats and dogs, but induced significant anorexia and growth depression in rabbits starting with 200 mg/kg/day orally. The [illegible] [illegible] dogs was [illegible] 300 mg/kg. Signs of acute [illegible] [illegible] were emesis, restlessness, pallor of

mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended adult oral dose is 20 mg once a day at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome, multiple endocrine adenomas)

The dosage of PEPCID in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q 6 h. In some patients a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q 6 h have been administered to some patients with severe Zollinger-Ellison Syndrome.

Concomitant Use of Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency

In patients with severe renal insufficiency [illegible] with a creatinine clearance less than 10 mL/min [illegible] elimination half-life of PEPCID may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dose of PEPCID may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

HOW SUPPLIED

[illegible] 3535—PEPCID Tablets, 20 mg [illegible] [illegible] MSD 963. They are [illegible]

NDC 0006-0963-[illegible] bottles of 30
NDC 0006-0963-28 unit dose package of 100.

No. 3536—PEPCID Tablets, 40 mg, are light brownish-[illegible] tablets coded MSD 964. They are [illegible]

NDC [illegible]
NDC [illegible]

[illegible]
[illegible]

MSD MERCK SHARP & DOHME

Issued October 1986

Printed in USA

[redacted] [redacted]

SEP 30 1986

NDA 19-462

Merck Sharp and Dohme Research Laboratories
Attention: Girard Picot, Ph.D.
Division of Merck and Co., Inc.
West Point, PA 19486

Dear Dr. Picot:

Please refer to your June 24, 1985 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pepcid (famotidine) Tablets.

We also acknowledge receipt of your amendments dated August 9, September 30 (two), October 15 and 24, November 7, 13, 18 and 22; December 13, 18 and 26, 1985; January 9, 10, 14 and 16; February 14 and 24; March 4, 18 (two) and 27; April 3, 5 and 21; May 7 and 22; August 7; and September 26, 1986.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit final printed labeling for the drug. The labeling should be consistent with the content of the enclosed marked up draft and should address the following issue: The decrease in drug clearance and increased half-life with decreased renal function is well-documented. Your dosage recommendation is to adjust for this by increasing the dosing interval to 36-48 hours. It is not obvious that this is the best possible response, i.e., the one that would best match the effect of a 40 mg HS dose in normals, i.e., a dose reduction to 30 mg would also be possible. Please examine these alternatives, simulating them as necessary, and reconsider the dosing recommendation. If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

In addition to final printed labeling, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Cardio-Renal Drug Products and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Labeling, HFN-240
Room 108-04
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit twelve copies of the printed labels and other labeling seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Constance Burner Henry
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Enclosure


MED
REV

Medical Officer's Review
NDA 19-462, Pepcid (famotidine)

Attachments: Package insert
Reprint of paper by Howard et al

12-31-85

New Drug Application NDA 19-462
Merck Sharp & Dohme Research Laboratories
Tablets PEPCID™ (Famotidine, MSD)

Item II - Summary of Application

A. Annotated Package Circular

A.H.F.S. Category: 56:40

MSD| Tablets PEPCID™ XXXXX

(Famotidine, MSD)

PEPCID™

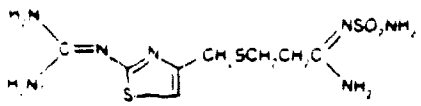
(Famotidine, MSD)

DESCRIPTION[1]

The active ingredient in Tablets PEPCID* (Famotidine, MSD), is a histamine H_2 receptor antagonist.

Famotidine is 3-[[[2- [(aminoiminomethyl) amino]-4-thiazoyl] methyl]thio]-N-(aminosulfonyl) -propanimidamide.

The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.43. Its structural formula is:



famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc, titanium dioxide.

1. Chemistry, Manufacturing and Controls
**Item II. D. 1. Vol. 1.1, p. 25
Item III. A. 8. Vol. 1.2, p. 08

** All annotations will have two references. The first reference is to Item II-Summary of Application contained in this volume. The page number indicates where a brief description can be found. The second reference is to a specific technical section and gives the volume and page number where a detailed description can be found.

PEPCID™
(Famotidine, MSD)

CLINICAL PHARMACOLOGY

GI Effects: PEPCID is a competitive inhibitor of histamine H_2-receptors.[2] The primary clinically important pharmacologic activity of PEPCID is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by PEPCID,[3] while changes in pepsin secretion are proportional to volume output.[4]

In both normal volunteers and hypersecretors, PEPCID inhibited basal, nocturnal[3,7] and daytime gastric secretion,[3,5] as well as secretion stimulated by ~~a variety of stimuli, such as~~ pentagastrin[4,6,8] ~~and food.[3,5]~~ After oral administration, the onset of the antisecretory effect occurred within one hour;[3,4,5,7] the maximum effect was dose-dependent, occurring within one to three hours.[3,4,6] Duration of inhibition of secretion was 10 to 12 hours.[3,7] After intravenous administration, the maximum effect was achieved within 30 minutes.[8] Single oral doses of 20 and 40 mg inhibited basal, 2nd nocturnal acid secretion in all subjects; mean gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours.[3] Similar doses given in the morning

2. Preclinical Pharmacology
   Item II. D. 2. Vol. 1.1, p. 29
   Item IV. A. 1. Vol. 1.3, p. 01

3. Ryan Study No. 8
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1819

4. Smith Study No. 2
   Item II. D. 4. Vol. 1.1, p. 87
   Item VII. F. 1. a. ii. Vol. 1.31, p. 1518

5. Ryan Study No. 7
   Item II. D. 4. Vol. 1.1, p. 88
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1748

6. McCallum Study No. 3
   Item II. D. 4. Vol. 1.1, p. 87
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1583

7. Cohen Study No. 5
   Item II. D. 4. Vol. 1.1, p. 88
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1668

8. Hunt Study No. 725
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1917

PEPCID™
(Famotidine, MSD)

CLINICAL PHARMACOLOGY (cont'd)

suppressed food-stimulated acid secretion in all subjects, with mean suppression of 76% and 84%, respectively, 3 to 5 hours after drug, and of 25% and 30%, respectively, 8 to 10 hours after drug; however, in some subjects who received the 20 mg dose, the antisecretory effect was dissipated earlier, within 6-8 hours.[9] There was no cumulative effect with repeated doses.[10] The basal nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of PEPCID to mean values of 5.0 and 6.4, respectively.[9,11] When PEPCID was given in the morning, the ~~basal~~ daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of PEPCID was raised to about 5.0.[9,11]

Fasting or postprandial serum gastrin levels may be slightly elevated during periods of drug antisecretory effect,[12,13] and with chronic therapy, an increase in gastric bacterial flora may occur.[14] Gastric emptying and exocrine pancreatic function are not affected by PEPCID.[15]

9. Ryan Study No. 6
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1819

10. Ryan Study No. 7
   Item II. D. 4. Vol. 1.1, p. 88
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1748

11. Smith Study No. 51
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.33, p. 1975

12. Zinny Study No. 1
   Item II. D. 4. Vol. 1.1, p. 91
   Item VII. F. 1. a. i. Vol. 1.30, p. 1050

13. Smith Study No. 2
   Item II. D. 4. Vol. 1.1, p. 87
   Item VII. F. 1. a. ii. Vol. 1.31, p. 1518

14. Cattau Study No. 12
   Item II. D. 4. Vol. 1.1, p. 92
   Item VII. F. 1. a. iii. Vol. 1.33, p. 2101

15. Redinger Study No. 61
   Item II. D. 4. Vol. 1.1, p. 92
   Item VII. F. 1. a. iii. Vol. 1.33, p. 2035

PEPCID™
(Famotidine, MSD)

Other effects: Systemic pharmacologic effects of PEPCID in the CNS, cardiovascular, respiratory or endocrine systems have not been found to date.[16,22,23] Serum prolactin levels do not rise after intravenous bolus doses of 20 mg PEPCID[17] and no antiandrogenic effects have been detected.[18,19]

Pharmacokinetics

PEPCID is incompletely absorbed.[17,21] The bioavailability of oral doses is 40–45%.[17] Bioavailability may be slightly increased by food, or slightly decreased by antacids;[20] however, these effects are of no clinical consequence. PEPCID undergoes minimal first-pass metabolism.[21] After oral doses, peak plasma levels occur in 1–3 hours.[17,21,22] Plasma levels after multiple doses are similar to those after single doses.[23,25] Fifteen to 20% of PEPCID in plasma is protein bound.[24] PEPCID has an elimination half-life of 2.5–3.5 hours.[17,22,23] PEPCID is eliminated by renal (65–70%)[17] and metabolic (30–35%) routes.[17,21] Renal clearance is 250–450 mL/min., indicating some tubular excretion.[17,22,23]

16. Shrivastava Study No. 31
    Item II. D. 4. Vol. 1.1, p. 91
    Item VII. F. 1. a. iii. Vol. 1.33, p. 219
17. Williams Study No. 42
    Item II. D. 3. Vol. 1.1, p. 52
    Item V. M. 12. Vol. 1.22, p. 259
18. Jensen Study No. 6
    Item II. D. 4. Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. Vol. 1.39, p. 402
19. Cohen Study No. 41
    Item II. D. 4. Vol. 1.1, p. 129
    Item VII. F. 2. a. iii. Vol. 1.38, p. 413
20. Kann Study No. 47
    Item II. D. 3. Vol. 1.1, p. 76
    Item V. M. 24. Vol. 1.25, p. 1316
21. Rotmensch Study No. 40
    Item II. D. 3. Vol. 1.1, p. 64
    Item V. M. 19. Vol. 1.23, p. 776
22. Zinny Study No. 1
    Item II. D. 3. Vol. 1.1, p. 67
    Item V. M. 20. Vol. 1.24, p. 843
23. De Schepper Study No. 748
    Item II. D. 3. Vol. 1.1, p. 54
    Item V. M. 15. Vol. 1.22, p. 388
24. Lin MSDRL Study
    Item II. D. 3. Vol. 1.1, p. 72
    Item V. M. 21. Vol. 1.24, p. 959
25. Williams Study No. 48
    Item II. D. 3. Vol. 1. 1, p. 70
    Item V. M. 25. Vol. 1.25, p. 1400

PEPCID™
(Famotidine, MSD)

Pharmacokinetics (cont'd)

Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound.[26,27] The only metabolite identified in man is the S-oxide.[28] There is a close relationship between creatinine clearance values and the elimination half-life of PEPCID.[29,30] In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min., PEPCID elimination half-lives may exceed 20 hours and adjustment of dosing intervals may be necessary[29] (see PRECAUTIONS, DOSAGE AND ADMINISTRATION) In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of PEPCID.[30]

26. Williams Study No. 42
Item II. D. 3. Vol. 1.1, p. 52
Item V. M. 12. Vol. 1.22, p. 259

27. Rotmensch Study No. 40
Item II. D. 3. Vol. 1.1, p. 64
Item V. M. 19. Vol. 1.23, p. 776

28. Yamada Yamanouchi Study
Item II. D. 3. Vol. 1.1, p. 67
Item V. M. 8 Vol. 1.22, p. 218

29. Abraham Study No. 404
Item II. D. 3. Vol. 1.1, p. 58
Item V. M. 17 Vol. 1.23, p. 639

30. Martin Study No. 744
Item II. D. 3. Vol. 1.1, p. 78
Item V. M. 16 Vol. 1.23, p. 450

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Clinical Studies

Duodenal Ulcer

In a U.S. multicenter, double-blind study[31] in outpatients with endoscopically confirmed duodenal ulcer, PEPCID ~~given as~~ 40 mg h.s. was compared to placebo. As shown in the table below, most patients treated with PEPCID were healed by Week 4.

31. U.S. Multicenter Trial vs. Placebo Acute Phase
Item II. D. 4. Vol. 1.1, p. 96
Item VII. F. 2. a. i. Vol. 1.35, p. 2922

Outpatients with endoscopically confirmed healed ulcers

	PEPCID 40 mg h.s. (N = 89)	Placebo h.s. (N = 97)
Week 2	*32 %	17 %
Week 4	*70 %	31 %

* statistically significantly different than placebo ($p < 0.001$)

Patients not healed by Week 4 were continued in the study. By Week 8, the incidence of healing ~~rate~~ was 83% for patients on therapy with PEPCID versus 45% for patients on placebo. The ~~rate~~ incidence of ulcer healing with PEPCID was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients on PEPCID than for patients on placebo; patients on PEPCID also took less antacid than the patients on placebo, but the difference was not clinically meaningful.

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Long-Term Maintenance Treatment of Duodenal Ulcers

The efficacy of a dosage regimen of PEPCID, 20 mg h.s. in the prevention of duodenal ulcer recurrence was compared to placebo h.s. in a U.S. double-blind, multicenter study[32] of patients with endoscopically confirmed healed duodenal ulcers. Following 6 months of therapy, PEPCID was significantly more effective ($p < 0.01$) than placebo in preventing ulcer recurrence. Of the 49 patients who completed up to 24 weeks of therapy with PEPCID 20 mg h.s., 22% of patients on PEPCID experienced ulcer recurrence, as compared to 55% of 62 patients on placebo. ~~In this clinical trial, patients have been maintained on this regimen for up to one year~~.

32. U.S. Multicenter Trial
vs. Placebo
Maintenance Phase
Item II. D. 4. Vol. 1.1, p. 108
Item VII. F. 2. a. i. Vol. 1.35, p. 2923

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Gastric Ulcer

In an international double-blind multicenter, study[33] in patients with endoscopically confirmed ~~acute benign~~ gastric ulcers, PEPCID, 40 mg h.s., was compared to placebo h.s. As illustrated in the table below, the ~~rate~~ incidence of ulcer healing with PEPCID was statistically significantly different than placebo, after 4 weeks to 8 weeks of therapy, based on proportion of endoscopically confirmed healed ulcers.

Patients with endoscopically confirmed healed ulcers

	PEPCID 40 mg h.s. (N = 149)	Placebo h.s. (N = 145)
Week 4	*47 %	31 %
Week 6	*65 %	46 %
Week 8	*80 %	54 %

* statistically significantly different than placebo ($p < 0.01$)

In this study, relief of daytime and nighttime pain was quicker for patients on therapy with PEPCID than for patients on placebo; patients on therapy with PEPCID also took antacids significantly less frequently than the patients on placebo, but the difference was not clinically meaning ful.

33. International Multicenter Trial vs. Placebo
Item II. D. 4. Vol. 1.1, p. 117
Item VII. F. 2. a. ii. Vol. 1.37, p. 3615

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Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome) ~~Multiple Endocrine Adenomas)~~

In studies[34,35] of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome ~~and multiple endocrine adenomas,~~ PEPCID significantly inhibited gastric acid secretion and controlled associated symptoms. Doses from 20 ~~mg q.i.d. to~~ 160 mg q 6h maintained basal acid secretion below 10 mEq/hr.; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. PEPCID was well tolerated at these high dose levels for prolonged periods (greater than 12 months) and there were no cases reported of gynecomastia, increased prolactin levels, or impotence.

34. Jensen Study No. 6
    Item II. O. 4. Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

35. Cohen Study No. 41
    Item II. O. 4. Vol. 1.1, p. 129
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4136

PEPCID™
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INDICATIONS AND USAGE

PEPCID is indicated in:

1. Treatment of acute duodenal ulcer.[34,37]

   Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 8 weeks.

2. Prophylactic use in duodenal ulcer disease[38,39]

3. Treatment of acute benign gastric ulcer.[40,41]

   Most patients heal within 8 weeks.

4. Treatment of ~~pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)~~.[42,43]

36. U.S. Multicenter Trial vs. Placebo Acute Phase
    Item II. D. 4. Vol. 1.1, p. 96
    Item VII. F. 2. a. i. Vol. 1.35, p. 2922

37. International Multicenter Trial vs. Ranitidine
    Item II. D. 4. Vol. 1.1, p. 102
    Item VII. F. 2. a. i. Vol. 1.36, p. 3283

38. U.S. Multicenter Trial vs. Placebo Maintenance Phase
    Item II. D. 4. Vol. 1.1, p. 108
    Item VII. F. 2. a. i. Vol. 1.35, p. 2923

39. International Multicenter Trial vs. Placebo
    Item II. D. 4. Vol. 1.1, p. 113
    Item VII. F. 2. a. i. Vol. 1.36, p. 3475

40. International Multicenter Trial vs. Placebo
    Item II. D. 4. Vol. 1.1, p. 117
    Item VII. F. 2. a. ii. Vol. 1.37, p. 3615

41. Yamanouchi Multicenter Trial vs. Gefarnate
    Item II. D. 4. Vol. 1.1, p. 123
    Item VII. F. 2. a. ii. Vol. 1.3[illegible] p. 3774

42. Jensen Study No. 6
    Item II. D. 4. Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

43. Cohen Study No. 41
    Item II. D. 4. Vol. 1.1, p. 129
    Item VII. F. 2. a. iii. Vol. 1.3[illegible], p. 4136

PEPCID™
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CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

PRECAUTIONS

General

Symptomatic response to therapy with PEPCID does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency

Dosing intervals may need to be prolonged in patients with severe renal insufficiency (creatinine clearance < 10 mL/min) to adjust for the longer elimination half-life of famotidine.[44] (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). However, no drug-related toxicity has been found with high plasma concentrations of famotidine.[45]

44. Abraham Study No. 404
Item II. D. 3. Vol. 1.1, p. 58
Item V. M. 17. Vol. 1.23, p. 639

45. Jensen Study No. 6
Item II. D. 4. Vol. 1.1, p. 127
Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

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(Famotidine, MSD)

Drug Interactions

No drug interactions have been identified. Studies with famotidine in man, in animal models,[46] and in vitro[47] have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man have included warfarin,[48] theophylline,[49] phenytoin,[50] diazepam,[51] aminopyrine[52] and antipyrine.[52] Indocyanine green as an index of hepatic blood flow and/or hepatic drug extraction has been tested and no significant effects have been found.[50]

46. Preclinical Pharmacology
    Item II D. 2. Vol. 1.1, p. 33
    Item IV. D. 2. (19) Vol. 1.5, p. 1232

47. Preclinical Pharmacology
    Item II D. 2. Vol. 1.1, p. 33
    Item IV D. 2. (20) Vol. 1.5, p. 1257

48. Ryan Study No. 53
    Item II D. 3. Vol. 1.1, p. 84
    Item VII. F. 1. a. iv. Vol. 1.34, p. 2725

49. Williams Study No. 48
    Item II D. 3. Vol. 1.1, p. 82
    Item VII. F. 1. a. iv. Vol. 1.34, p. 2375

50. Williams Study No. 55
    Item II D. 3. Vol. 1.1, p. 83
    Item VII. F. 1. a. iv. Vol. 1.34, p. 2472

51. Zinny Study No. 58
    Item II D. 3. Vol. 1.1, p. 81
    Item VII. F. 1. a. iv. Vol. 1.33, p. 2284

52. Langman Study No. 690
    Item II D. 3. Vol. 1.1, p. 80
    Item VII. F. 1. a. iv. Vol. 1.33, p. 2201

PEPCID™
(Famotidine, MSD)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 106 week study[53] in rats and a 92 week study[54] in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the maximum recommended human dose), there was no evidence of carcinogenic potential for PEPCID.

Famotidine was negative in the microbial mutagen test (Ames test) using Salmonella typhimurium and Escherichia coli with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate.[55] In in vivo studies in mice with a micronucleus test[56] and a chromosomal aberration test[57], no evidence of a mutagenic effect was observed.

In studies with rats given oral doses[58] of up to 2000 mg/kg/day or intravenous doses[59] of up to 200 mg/kg/day (approximately 2500 and 250 times the maximum recommended human dose, respectively), fertility and reproductive performance were not affected.

53. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 41
Item IV. D. 6. (3). Vol. 1.19, p. 6510

54. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 41
Item IV. D. 6. (2). Vol. 1.18, p. 6113

55. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 40
Item IV. D. 5. (1). Vol. 1.17, p. 5817

56. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 40
Item IV. D. 5. (12). Vol. 1.17, p. 5972

57. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 40
Item IV. D. 5. (13). Vol. 1.17, p. 5985

58. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 37
Item IV. D. 4. (11). Vol. 1.15, p. 4997

59. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (12). Vol. 1.16, p. 5266

PEPCID™
(Famotidine, MSD)

Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats [60,61] and rabbits [62,63] at oral doses of up to 2000 and 500 mg/kg/day, respectively (approximately 2500 and 625 times the maximum recommended human dose, respectively), and have revealed no evidence of impaired fertility or harm to the fetus due to PEPCID. There are, however, no adequate or well-controlled studies in pregnant women.

Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies performed in lactating rats have shown that famotidine is secreted in breast milk.[64] It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from PEPCID, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

60. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 37
Item IV. D. 4. (1). Vol. 1.12, p. 4106

61. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (2). Vol. 1.13, p. 4144

62. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (5). Vol. 1.14, p. 4671

63. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (6). Vol. 1.15, p. 4753

64. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 33
Item IV. D. 2. (15). Vol. 1.5, p. 1187

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Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

No dosage adjustment is required based on age[65] (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

65. Martin Study No. 744
Item II. D. 3. Vol. 1.1, p. 78
Item VII. F. 1. a. i. Vol. 1.31, p. 1228

ADVERSE REACTIONS[66]

PEPCID is usually well tolerated; most adverse reactions have been mild and transient. The adverse reactions listed below have been reported during domestic and international clinical trials in 2089 patients. In those controlled clinical trials in which PEPCID was compared to placebo, the ~~overall~~ incidence of adverse experiences in the group which received PEPCID 40 mg at bedtime was similar to that in the placebo group. No antiandrogenic or other adverse hormonal effects have been observed.

66. Safety Summary
Item II. D. 4. Vol. 1.1, p. 131
Item VII. C. 2. Vol. 1.27, p. 218

The following adverse reactions have been reported ~~at a rate of greater~~ to occur in more than 1% ~~in~~ of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.2%), dizziness (1.1%), constipation (1.2%) and diarrhea (1.2%).

ADVERSE REACTIONS (cont'd)

Other reactions have been reported in clinical trials but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: palpitations

Gastrointestinal: nausea, vomiting, abdominal discomfort, anorexia, dry mouth

Hypersensitivity: orbital edema

Musculoskeletal: musculoskeletal pain, arthralgia

Nervous System/Psychiatric: paresthesias; psychic disturbances including depression, anxiety, decreased libido; insomnia, somnolence

Respiratory: bronchospasm

Skin: alopecia, acne, pruritus, rash, dry skin, flushing

Special Senses: tinnitus, taste disorder

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OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects[67] In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD_{50} of famotidine in male and female rats and mice was greater than 3000 mg/kg.[68]

DOSAGE AND ADMINISTRATION[69]

Duodenal Ulcer

~~Acute Therapy~~ Healing: The recommended adult oral dosage ~~for acute duodenal ulcer~~ is 40 mg once a day at bedtime. Treatment should be given for 4–8 weeks, but the duration of treatment may be shortened if healing can be documented. Healing occurs within 4 weeks in most cases ~~of duodenal ulcer~~.

67. Jensen Study No. 6
    Item II. D. 4. Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. Vol. 1.33, p. 4028

68. Preclinical Toxicology
    Item II. D. 2. Vol. 1.1, p. 34
    Item IV. A. 3. b. i. Vol. 1.3, p. 38

69. Dosage and Administration Summary
    Item II. D. 4. Vol. 1.1, p. 86
    Item VII. B. 2. Vol. 1.27, p. 32

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Maintenance ~~Therapy~~: For the prevention of recurrence ~~of duodenal ulcer, it is recommended that therapy with PEPCID be continued with~~ a dose of 20 mg once a day at bedtime, is recommended.

~~Benign Gastric Ulcer~~

~~Acute Therapy~~ Healing: The recommended adult oral dosage ~~for acute benign gastric ulcer~~ is 40 mg once a day at bedtime. ~~Treatment should be given~~ for 4 to 8 weeks, depending on when ~~but the duration of treatment may be shortened if~~ healing can be documented.

PEPCID®
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~~Pathological Hypersecretory Conditions~~

~~(such as~~ Zollinger-Ellison Syndrome~~, multiple endocrine adenomas)~~

The dosage of PEPCID ~~in patients with pathological hypersecretory conditions~~ varies with the individual patient. The recommended adult oral starting dose ~~for pathological hypersecretory conditions~~ is 20 mg q6h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q6h have been administered to some patients~~, with severe Zollinger-Ellison syndrome~~.

Concomitant Use ~~with~~ of Antacids[70]

Antacids may be given concomitantly if needed.

70. Kann Study No. 47
Item II. D. 3. Vol. 1.1, p. 76
Item V. M. 24. Vol. 1.25, p. 13

Dosage Adjustment for Patients with Severe Renal Insufficiency

In patients with severe renal insufficiency, i.e., with a creatinine clearance less than 10 mL/min., the elimination half-life of PEPCID may exceed 20 hours, reaching approximately 24 hours in anuric patients.[71] Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosing interval of PEPCID may be prolonged to 36–48 hours as indicated by the patient's clinical response.

71. Abraham Study No. 404
Item II. D. 3. Vol. 1.1, p. 58
Item V. M. 17. Vol. 1.23, p. 6

HOW SUPPLIED[72]

Tablets PEPCID are "D"-shaped, film-coated tablets supplied as follows:

No. XXXX - 20 mg beige colored, coded MSD 963.

NDC 0006-0963-30 unit of use bottles of 30

NDC 0006-0963-61 unit of use bottles of 60

NDC 0006-0963-28 unit dose package of 100.

No. XXXX - 40 mg light brownish orange, coded MSD 964.

NDC 0006-0964-30 unit of use bottles of 30

NDC 0006-0964-61 unit of use bottles of 60

NDC 0006-0964-28 unit dose package of 100.

MSD MERCK SHARP & DOHME
DIV OF MERCK & CO., INC.
WEST POINT, PA. 19486, USA

Issued Printed in USA

72. Chemistry, Manufacturing and Controls
Item II. D. 1. Vol. 1.1, p. 027
Item III. B. 4 Vol. 1.2, p. 109

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA 19-462

Name of Drug: Pepcid (famotidine)

Sponsor: Merck Sharp & Dohme Research Laboratories

Formulation: Tablets 20 mg and 40 mg.

Route of Administration: Oral

Proposed Clinical Use: Treatment of peptic ulcer disease.

Pharmacological Class: H_2-blocker.

Date of Submission: June 24, 1985

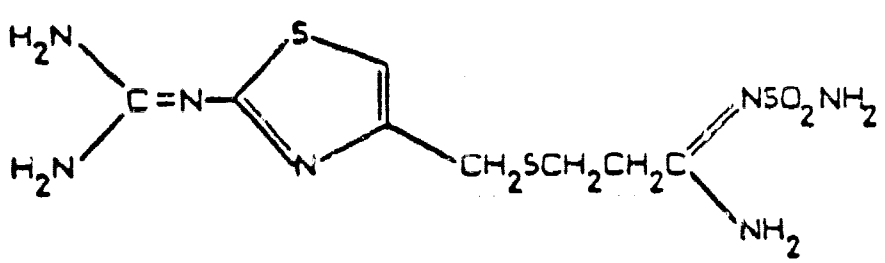
Material Submitted for Clinical Review:

Volume 1.1:	Summary of clinical reports
Volumes 1.27-1.38:	Full clinical reports
Volumes 1.49-1.53:	Case report forms on microfiche

Date Review Completed: 6 December 1985.

Reviewer: William H. Bachrach, M.D.

I. Background/Rationale: Famotidine, 3-[[[2-[(amino-iminomethyl) amino] 4-thiazolyl] methyl] thio]-M-(aminosulfonyl)-propanimidamide, with the following structural formula



is a long-acting H_2-blocker developed by Yamanouchi Pharmaceutical Company, Ltd., and licensed to Merck & Company, Inc. for distribution outside of Japan.

H_2-blockers inhibit gastric acid secretion and, primarily by this action, accelerate healing of peptic ulcers. Two H_2-blockers have been approved for marketing in the U.S., the first cimetidine, the second ranitidine. The use of H_2-blockers in patients with peptic ulcer disease has resulted in decreased patient morbidity and, according to some reports, in the need for elective operations, but the incidence of surgery for complications has not diminished.

Famotidine has been shown in animal and human studies to inhibit basal and stimulated gastric acid secretion. Based on these data, doses of famotidine have been selected for the evaluation of its effectiveness and safety in patients with peptic ulcer disease. Because of its long duration of action, it is expected that a once-a-day bedtime regimen will be effective.

No marketing experience is available because famotidine had not been marketed in any country at the time of submission of this NDA.

II. Clinical Pharmacology

A. Human tolerance

1. Japanese study

a. Title: An open study to assess safety, tolerability and drug levels in blood and urine of famotidine administered orally to normal male volunteers.

b. Investigators: T. Miwa, M.D. and M. Miwa, M.D., School of Medicine, Tokai University.

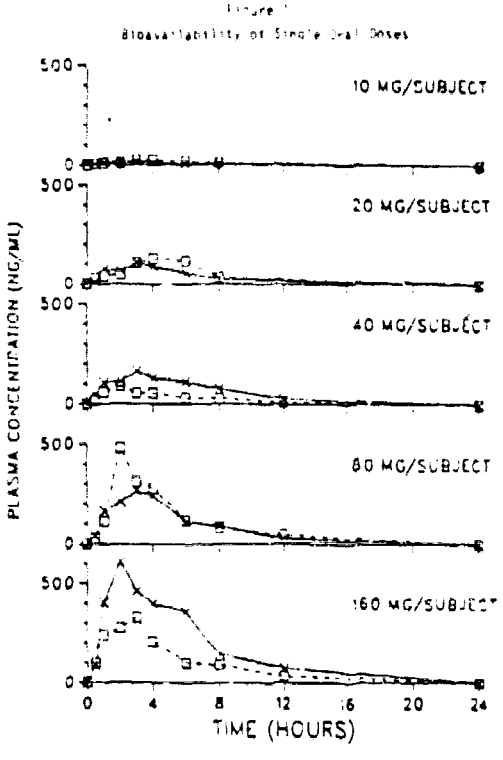
c. Design of study: doses of 5, 10, 20, 40, 80 and 160 mg were administered orally to each of 2 volunteers after the results of the preceding dose had been reviewed; 20 and 40 mg b.i.d. for 5 days were administered to 3 of the subjects after satisfactory completion of the single-dose sequence. The drug was administered on an empty stomach in the single-dose studies and 1/2 hour after meals in the repetitive dose study.

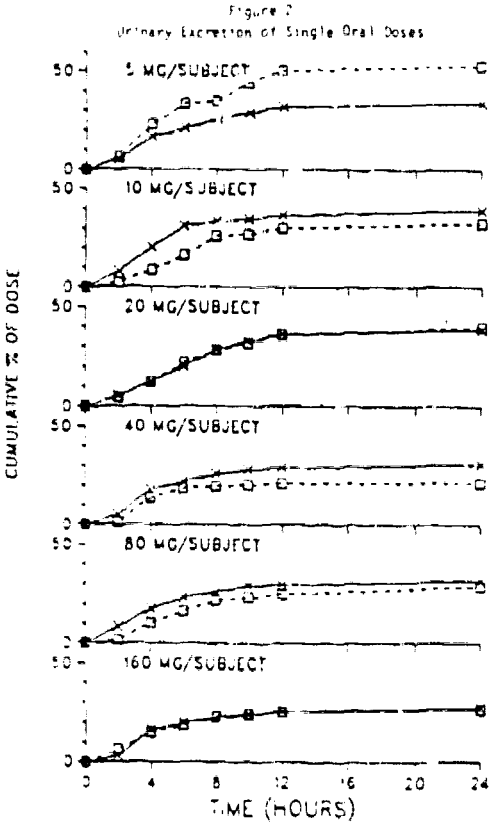
d. Results

(1) Safety: in none of the 12 volunteers were there any changes attributable to the drug in the vital signs, ECG, hemogram (including Coombs test), blood chemistry or urinalysis.

(2) Plasma concentration (figure 1): plasma levels, measurable with all except the 5 mg dose, were proportional to the size of the dose. Peak levels were reached between 2 and 3 hours. Drug levels were still detectible at 12 hours after doses of 40 mg and greater, but not at 24 hours at any of the single doses. No plasma accumulation of the drug was apparent in the multiple-dose studies.

(3) Urinary excretion (figure 2): the cumulative excretion of the drug amounted to 30-40% for all doses; most of the drug was excreted within the first 8 hours. After multiple dose administration, the daily excretion remained constant.





e. Conclusions: famotidine was well tolerated by healthy male volunteers when administered in single oral doses of 5 to 160 mg and in multiple 20 and 40 mg b.i.d. oral doses for 5 days. The drug was rapidly absorbed with peak levels at 2-3 hours proportional to the size of administered doses. Thirty to 40% of the drug was excreted in the urine; no accumulation was observed. No adverse effects were reported.

2. Study No. 1

a. Title: A double-blind, single, rising dose, placebo-controlled study to determine safety, tolerability and dose proportionality of blood and urine levels of famotidine administered orally to healthy volunteers.

b. Investigators: Miguel A. Zinny, M.D., Medical and Technical Research Associates, Needham, MA and Norman D. Grace, M.D., Tufts University School of Medicine, Boston.

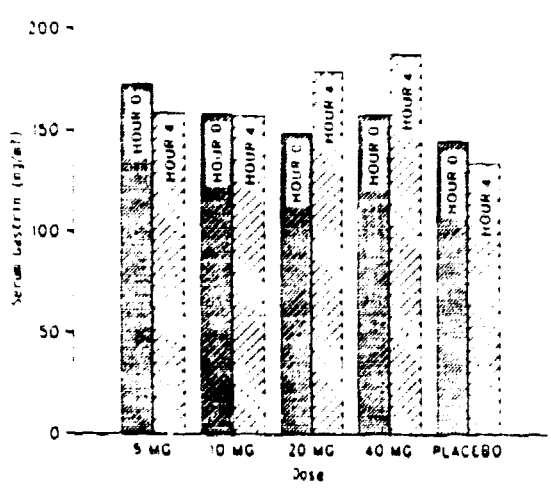
c. Design of study: in this placebo-controlled study in 15 healthy volunteers, the subjects were admitted to the Clinical Research Unit the evening preceding each treatment period and remained confined to the unit until completion of the 48-hour treatment period. Following an overnight fast, the subjects received a single oral dose of famotidine 5, 10, 20 or 40 mg with a placebo control interspersed randomly in one of the treatment periods. Study periods were separated by intervals of one week. Vital signs were measured at 0, 2, 4, 8, 12, and 24 hours post-dosing. Laboratory safety parameters, including ECGs, were assessed before and after 24 hours of treatment at each study period. Plasma and urine samples collected at appropriate intervals were frozen for analysis at the sponsor's laboratories. At appropriate intervals post-treatment the subjects were asked about any unusual symptoms. In this and many of the following studies, symptoms were graded:

None:	no awareness of abnormal signs or symptoms
Mild:	aware of symptoms, but easily tolerated
Moderate:	discomfort enough to interfere with but not prevent daily activity
Severe:	unable to perform usual daily activities

d. Results

(1) Safety parameters: no abnormalities of vital signs, hemogram, serum electrolytes or urinalysis were observed with either famotidine or placebo. One of the subjects experienced transient lightheadedness after placebo. There were no other clinical adverse events.

(2) Serum gastrin (figure 3): mean serum gastrin levels at 0 hour were higher for all doses of famotidine than placebo. Four hours after treatment, mean gastrin levels were statistically significantly higher after the 20 and 40 mg doses than after the lower doses and placebo.



(3) The results of serum prolactin determinations are described below under IID, "Hormonal effects."

e. Conclusions: famotidine is well-tolerated in single oral doses up to 40 mg. Doses of 20 mg and 40 mg increase serum gastrin.

3. Study No. 748

a. Title: A double-blind, placebo-controlled study to investigate the safety and tolerability of repeated doses of famotidine in healthy subjects.

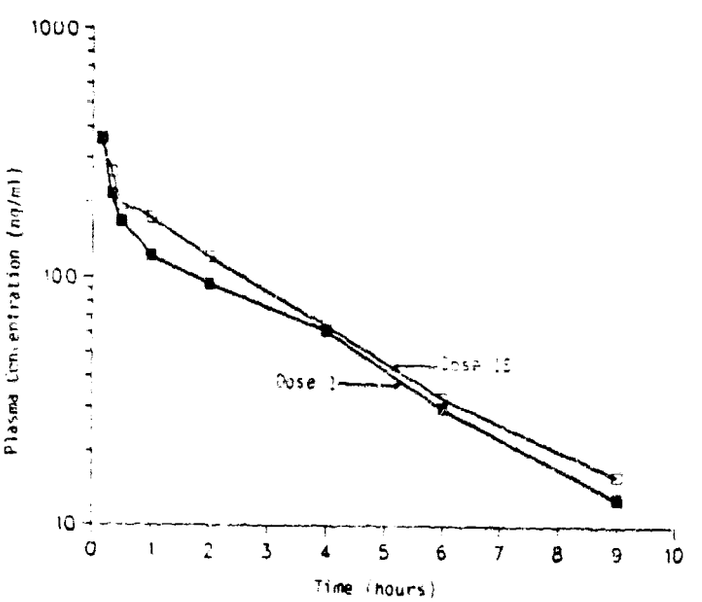
b. Investigator: Professor P. J. DeSchepper, Department of Pharmacology, Campus Gasthuisberg, Leuven, Belgium.

c. Design of study: at 0800 and 1700 hours for 7.5 days, the subjects received intravenous bolus injections of 5 ml containing either famotidine 20 mg (6 subjects) or placebo (2 subjects). Doses on odd-numbered days were administered in the left arm and on even numbered days in the right arm. Tolerability and safety were assessed by monitoring pain and induration at the injection site, ECG, vital signs, clinical chemistry, urinalysis, clinical adverse experiences and any changes in physical status. Plasma levels and urinary excretion of famotidine were determined after the first and 15th doses.

d. Results

(1) Plasma levels of famotidine (figure 4): the plasma is cleared rapidly of the administered drug with no evidence of a cumulative delay in clearance.

Figure 4
Mean Plasma Concentration of Famotidine
Following Single and Repeated I.V. Doses (N = 6)



(2) Safety: induration and local hyperemia occurred in 2 of the 6 famotidine treated subjects; in one of these, the investigator attributed the result to a slight extravasation of the drug during the last 15 seconds of the injection. Epigastric discomfort was reported by 3 famotidine and 1 placebo-treated subjects. A few laboratory safety parameters showed a statistically significant change after administration of both famotidine and placebo. No consistent changes were observed in physical examination or ECGs. A statistically significant decrease in systolic blood pressure was noted in subjects receiving placebo as well as in those receiving famotidine. Thus, clinical adverse experiences were few and they were similar for drug- and placebo-treated subjects.

e. Conclusions: famotidine 20 mg b.i.d. intravenously for 15 doses was well-tolerated in healthy subjects.

4. Summary of tolerance studies: In 3 studies in a total of 36 healthy volunteers famotidine was well tolerated in single oral doses up to 160 mg, in repetitive oral doses of 20 mg and 40 mg b.i.d. for 5 days, and in intravenous doses of 20 mg b.i.d. for 7.5 days. The only observation of possible clinical significance was a mild elevation of serum gastrin levels after oral administration of 20 and 40 mg. Additional tolerance data are derived from studies not designed primarily for this purpose.

B. Bioavailability/Pharmacokinetics

1. Study No. 748: the protocol has just been reviewed above under "Human Tolerance." The pharmacokinetic data derived from that study show (table 1) that after repeated administration of 20 mg twice daily for 15 doses, the drug was cleared primarily through the kidney and that the half-life was a little less than 3 hours.

TABLE 1

Pharmacokinetic parameters (geometric mean) of famotidine following repeat intravenous administration of 20 mg BID daily for 15 doses in healthy subjects.

Plasma Clearance, ml/min	313
Renal Clearance, ml/min	259
Non-renal Clearance* ml/min	54
Half-life, hours	2.7
Urinary Recovery, % of Dose	82.9

*Difference between plasma clearance and renal clearance.

2. Study No. 42

a. Title: An open, 4-way cross-over, single dose, comparative bioavailability study of famotidine capsules 20 mg, tablets 20 mg and 40 mg, and intravenous injection of 20 mg.

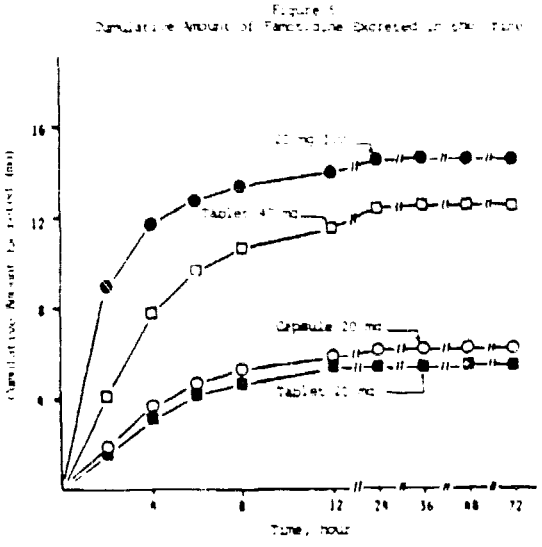
b. Investigator: Roger L. Williams, M.D., University of California, San Francisco, CA.

c. Design of study: this was an open, single-dose, 4-way cross-over study in 16 healthy volunteers assigned randomly to receive each of the 4 treatments listed in the title with a 1-week washout between treatments. Following administration of the test medications, plasma and urine samples were taken at appropriate intervals and were assayed for levels of famotidine.

d. Results

(1) Safety: no clinical or biochemical adverse experiences were reported at any time during the study.

(2) Pharmacokinetics: the time to maximum blood levels was the same for all 3 oral doses but reached a significantly higher level and remained higher for a longer period time with the 40 mg tablet. Approximately 30% of the drug was excreted in the urine over a 72 hour period after all 3 oral doses (figure 5), which was about half of the amount excreted after the intravenous dose. The total body clearance averaged approximately 28 l/h and the mean half-life was around 3 hours. For all practical purposes the 3 oral formulations had a similar bioavailability, approximating 45%.



e. Conclusions: single oral doses of famotidine, capsules 20 mg, tablets 20 mg or 40 mg, and IV dose of 20 mg, were well-tolerated. Systemic bioavailability approximated 45% and was similar for all 3 oral doses. The 20 mg capsule and 20 mg tablet are bioequivalent.

3. Study No. 556

a. Title: A two-part, open study in healthy elderly subjects to examine the pharmacokinetic profiles of famotidine when administered as a single intravenous and single oral dose (Part I) and repeated oral doses (Part II).

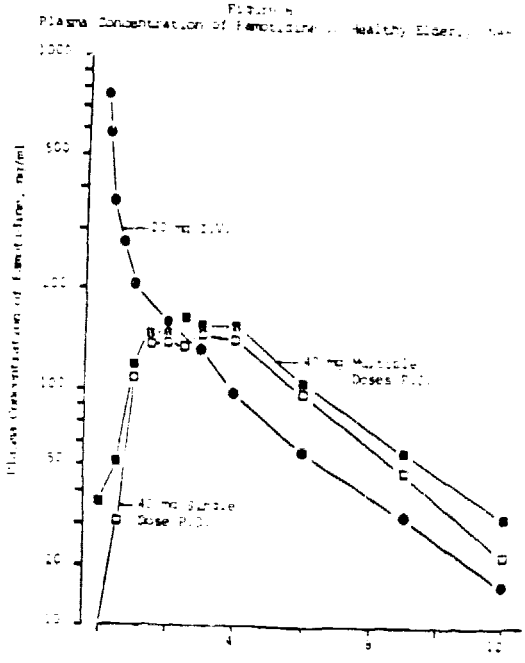
b. Investigator: B. Martin, M.D., Bios Consulting and Contract Research, Ltd., Surrey, England.

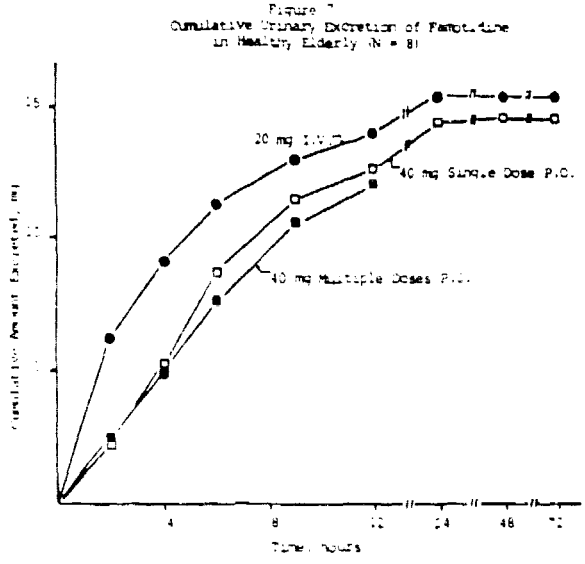
c. Design of study: open, two-part study in 8 healthy elderly subjects with random cross-over treatment sequence. During the first part of the study, fasting subjects received either a single intravenous dose of 20 mg or an oral dose of 40 mg. In the second part of the study they received 40 mg b.i.d. for 9 doses. Plasma and urine samples were collected according to the same schedule as that in the study reviewed above. Safety parameters were assessed by both clinical observation and conventional laboratory tests.

d. Results

(1) Safety: no drug-related adverse events were reported.

(2) Pharmacokinetics: plasma concentration of famotidine following the administration of a single oral dose or following the last of the multiple oral doses of 40 mg were similar (figure 6) as were the curves for urinary secretion of famotidine (figure 7). The disposition of the drug was therefore similar to that found in the younger volunteers reported in the study reviewed above. The bicavailability in these elderly subjects was 40%, i.e., in the same range as that in the younger subjects.





e. Conclusions: the results of this study indicate that famotidine is as safe and as bioavailable in healthy elderly subjects as in the younger age group.

4. Study No. 527

a. Title: An open study to assess the disposition kinetics and safety of famotidine in patients with moderate to severe renal insufficiency.

b. Investigators: Paul Abraham, M.D. and William F. Keane, M.D., Drug Evaluation Unit, Regional Kidney Disease Program, Hennepin County Medical Center, Minneapolis, MN.

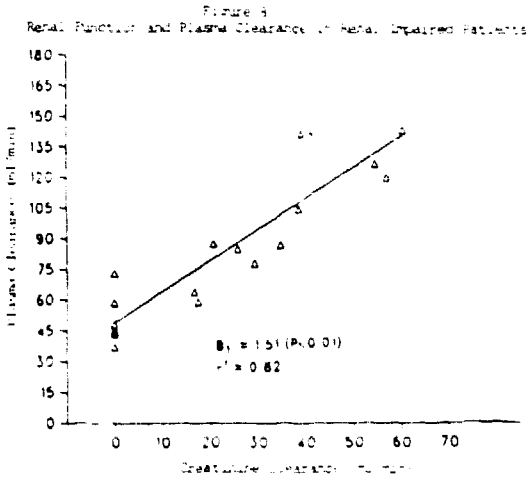
c. Design of study: 18 patients with moderate to severe renal insufficiency were assigned to one of three groups according to the degree of renal impairment. Group 1 (7 subjects) had a creatinine clearance of 30-50 ml/min and a serum creatinine greater than 3 mg %; the creatinine clearance in Group 2 (5 subjects) was 10-30 ml/min, in Group 3 (6 subjects) less than 10 ml/min. Patients in Group 3 were anuric; hemodialysis was disconnected one day prior to the administration of famotidine. On the study day a

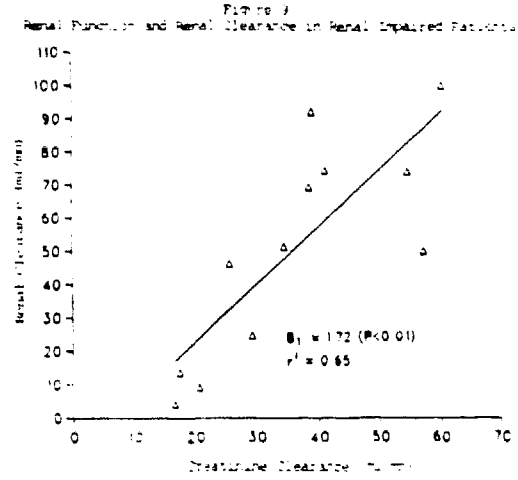
single intravenous injection of famotidine 10 mg was given over a 1 minute period. Plasma and urine samples were collected according to essentially the same schedule as in the protocols reviewed above. Insulin and creatinine clearances were determined for 30 minute periods 1.5 hours before and 4 hours after administration of the drug. The patients were observed for any adverse clinical reactions; conventional laboratory tests were performed before and after drug administration.

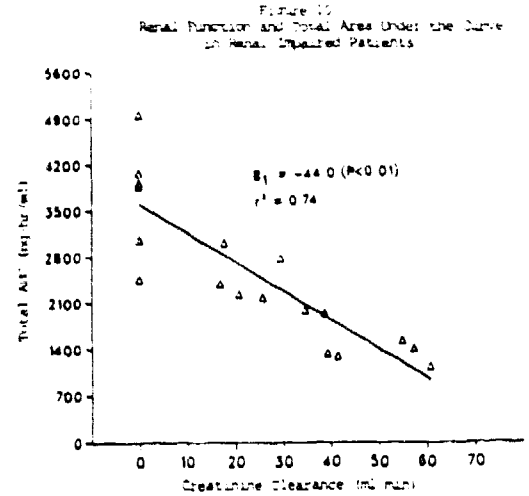
d. Results

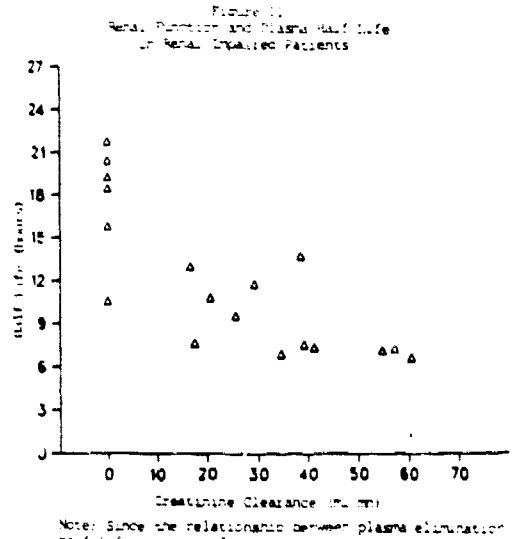
(1) Safety: no clinically important drug-related adverse events occurred during this study.

(2) Pharmacokinetics: in patients with impairment of renal function plasma clearance (figure 8) and renal clearance (figure 9) of the drug are diminished pari passu with the degree of renal impairment. The total area under the curve (figure 10) and the half-life (figure 11) are inversely proportional to the creatinine clearance. The non-renal clearance was not affected by the degree of impairment of renal function. Considering that the upper limit of half-life in healthy young and healthy elderly subjects was in the neighborhood of 5 hours, it is apparent that the half-life of famotidine becomes prolonged with a degree of renal impairment characterized by a creatinine clearance of less than 30 ml/min.





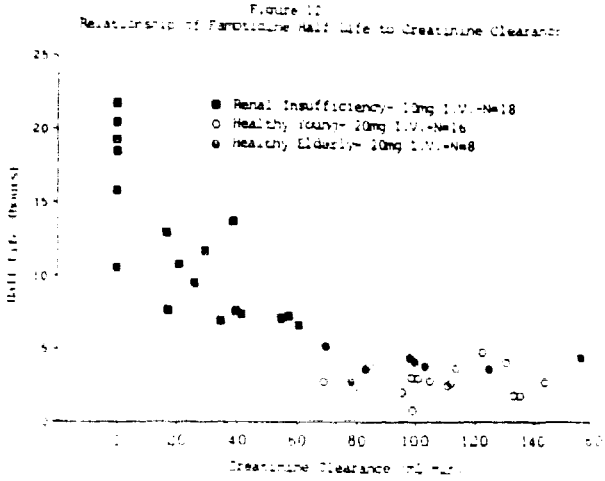




Note: Since the relationship between plasma elimination half-life and renal function is known to be non-linear, simple linear regression analysis was not performed.

e. Conclusion: the results of all parameters of disposition of famotidine in patients with decreased renal function indicate that in patients with creatinine clearance of less than 30 ml/min the dosage of famotidine must be adjusted downward to achieve blood levels comparable with those obtainable at any given dose in patients with normal renal function or with lesser degrees of renal impairment.

5. Summary of bioavailability/pharmacokinetic studies: the results of 4 studies evaluating famotidine in single intravenous doses of 10 mg and 20 mg, single oral doses of 10 mg, 20 mg and 40 mg, and multiple oral doses of 40 mg indicate that the drug is 40-45% bioavailable, has a mean half-life of about 3 hours and is cleared from the body primarily via the kidneys. The pharmacokinetics are approximately the same in elderly as in younger subjects, while in patients with renal insufficiency significant delay in excretion of the drug appears when the degree of renal impairment amounts to a creatinine clearance of less than 30 ml/min. A reduction in the famotidine dose would therefore be indicated in such patients. The comparative half-lives of famotidine in the healthy young, the healthy elderly and the renally-impaired subjects are shown graphically in figure 12. No drug-related adverse effects were documented in any of these studies.



C. Gastric and pancreatic function

1. Pentagastrin-stimulated gastric secretion

a. Study No. 725

(1) Title of study: Comparison of 3 different doses of famotidine on pentagastrin-stimulated gastric acid secretion.

(2) Investigator: Professor Richard H. Hunt, McMaster University Medical Centre, Hamilton, Canada.

(3) Design of study: double-blind, four-way, placebo-controlled, cross-over study in which 8 healthy volunteers were assigned randomly to receive 3 dosage regimens of famotidine intravenously to achieve plasma concentrations of 10, 30 and 90 ng/ml respectively, or placebo. In the morning after an overnight fast the subjects were intubated with a 14 French double-lumen tube, the contents of the stomach emptied, and continuous aspiration carried out for 7 consecutive hours. The first hour assessed basal acid secretion. A 19-gauge butterfly needle was then inserted into a vein in each forearm to provide for administration of pentagastrin and test drugs separately. A loading dose of famotidine was administered as a bolus injection over 2 minutes and constant infusion started immediately thereafter at a rate to provide the desired blood level. The amounts of famotidine administered were:

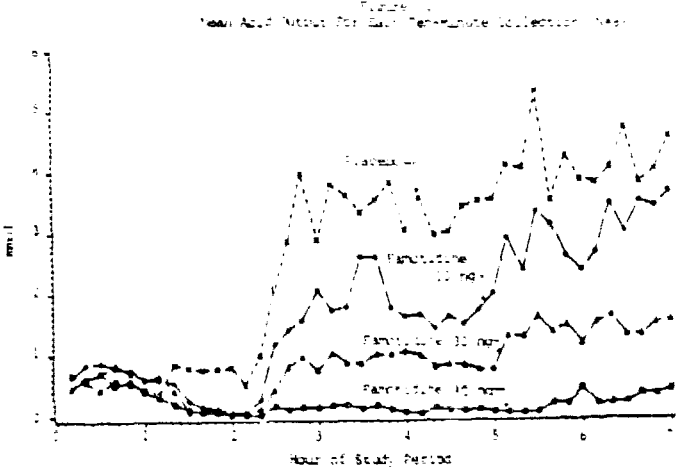
Plasma concentrations ng/ml	Loading dose (2 min) mcg/kg	Rate of infusion mcg/kg/hr
10	3	4.3
30	9	12.9
90	27	38.7

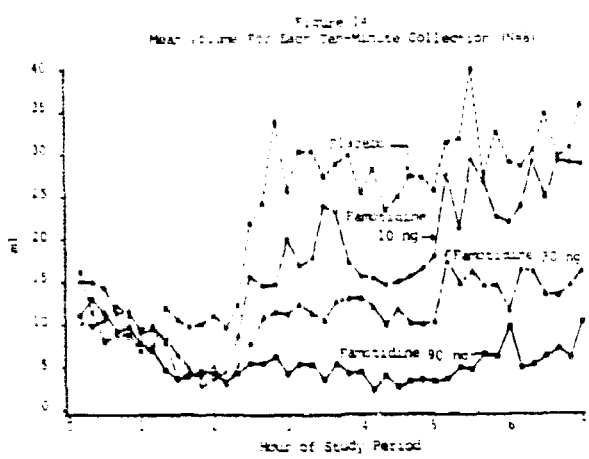
The placebo arm consisted of saline infused at a rate of 50 ml/h. At the end of the first 2 hours pentagastrin infusions were administered in 5 incremental infusion rates, each for a period of 1 hour, starting with 0.1 mcg/kg/h and ending with 2.0 mcg/kg/h. Blood samples for assay for famotidine were obtained at baseline and at hourly intervals for 7 hours. The volume of gastric secretion was measured every 10 minutes and analyzed for pH, titratable acidity and pepsin concentration. The first 30 minutes of each hour was considered a stabilizing stage; the collections of the last three 10-minute intervals of each hour were averaged and doubled to obtain the hourly rates of secretion. Observations to assess safety included a hemogram, clinical chemistry and urinalysis.

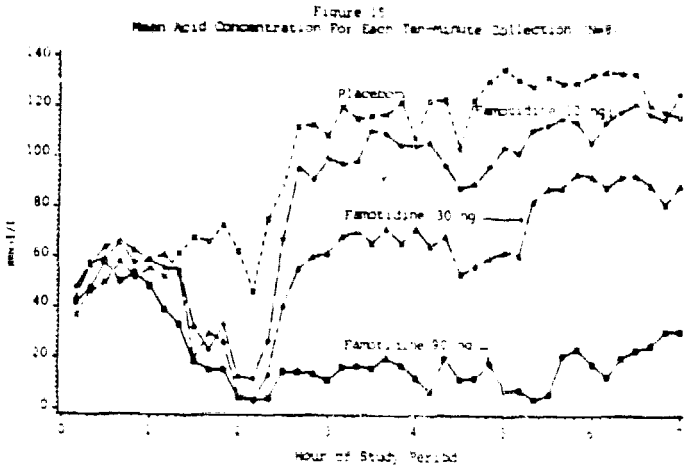
(4) Results

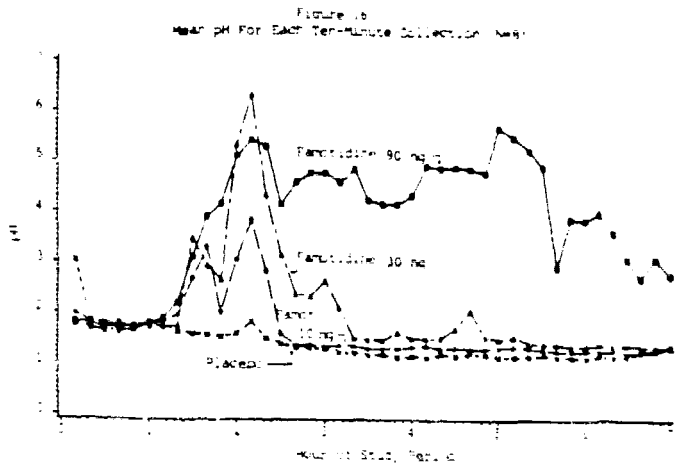
(a) Safety: no drug-related adverse events occurred during these studies.

(b) Gastric secretion: 8 volunteers completed the studies. During pentagastrin stimulation, famotidine significantly reduced gastric acid output in a dose-related fashion, reaching almost 100% inhibition with the highest plasma concentration of the drug (figure 13), an effect resulting from reduction in both the volume (figure 14) and the concentration (figure 15) of acid. Paradoxically, a sustained elevation of pH was observed with only the dose which yielded a blood level of 90 ng/ml (figure 16). Pepsin concentration was not significantly different with the 3 doses than with placebo, but as a result of the great reduction in volume the pepsin output was correspondingly reduced.









(5) Conclusions: constant intravenous infusions of famotidine at rates estimated to produce plasma concentrations of 10, 30, and 90 ng/ml inhibited basal gastric secretion maximally and pentagastrin-stimulated secretion in a concentration-dependent manner. At a concentration of 90 ng/ml acid secretion is almost completely inhibited. The sponsor concludes that for maximal therapeutic antisecretory effects, this level of plasma concentration might be desirable.

(6) Comment: the investigator must have had some basis for knowing a priori what rates of infusion would produce the desired blood levels. It will be interesting to hear from the sponsor how it was done.

b. Study No. 2

(1) Title: A double-blind, placebo and active controlled study to determine the effect of three separate incremental oral doses of famotidine on pentagastrin-stimulated gastric acid secretion in healthy volunteers.

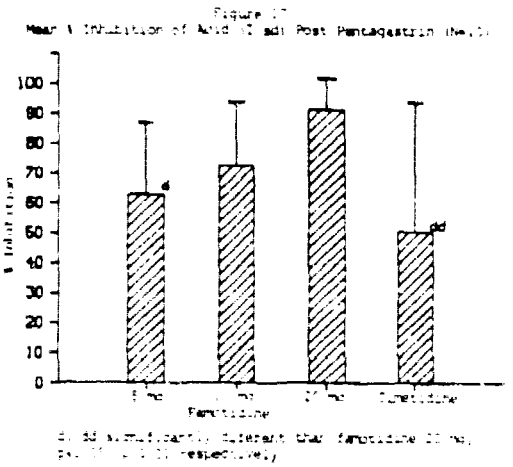
(2) Investigator: J. Lacey Smith, M.D., Baylor College of Medicine, Houston, TX.

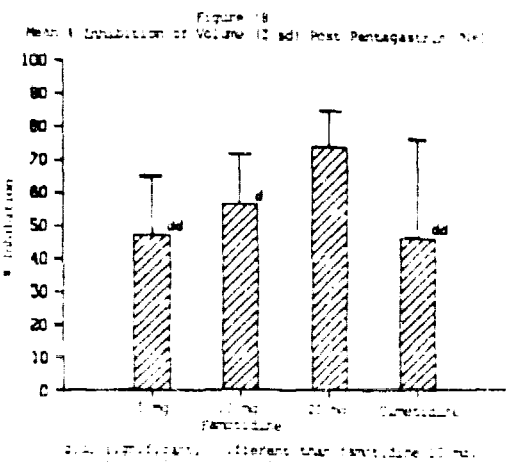
(3) Design of Study: double-blind, cross-over, placebo and active drug (cimetidine) controlled study. Ten healthy volunteers eligible for the study on the basis of medical history, physical examination, laboratory tests and ECGs received single doses of famotidine 5, 10, and 20 mg placebo, or cimetidine 300 mg all administered orally with water 200 ml. The subjects remained ambulatory for 1 1/4 hours and were then intubated with a 16 French double-lumen tube. Volume of secretions lost through the pylorus was corrected by infusion of a standard solution of phenol-red. Gastric aspirates were collected for three 15-minute intervals followed by IM injection of pentagastrin 6 ug/kg, followed by 15-minute collections of the continuously aspirated secretions for one hour. An additional investigation enlisted 6 of the volunteers who were found to be high basal acid secretors (more than 2.0 mEq/h) and/or brisk responders to pentagastrin (more than 20 mEq/h) in a study to assess the effect of famotidine 20 mg administered orally at 8 p.m. on the gastric secretory response to a single IM dose of pentagastrin given 10 and 12 hours later.

(4) Results

(a) Safety: no adverse events occurred during this study.

(b) Gastric secretion: pentagastrin-stimulated acid output was inhibited by famotidine in a dose-related fashion (figure 17), a result primarily of inhibition of volume of secretion (figure 18). The percent inhibition with cimetidine 300 mg was of the same order as that with famotidine 5 mg. Basal gastric secretion was decreased by all active treatments in comparison with placebo. Among the 6 subjects in the additional study, inhibition of pentagastrin-stimulated acid secretion 10-12 hours following famotidine 20 mg ranged from 18% to 88% with a mean of 53.6%.





(5) Conclusion: Famotidine administered orally approximately one hour before intramuscular injection of pentagastrin inhibited the gastric secretion in the following hour significantly more than did placebo with all doses tested. The inhibitory effect of famotidine 5 mg was comparable to that of cimetidine 300 mg. Famotidine 20 mg diminished the secretory response in varying degrees to an injection of pentagastrin given up to 11 hours later.

c. Study No. 3

(1) Title of Study: A double-blind placebo and active drug-controlled study to determine the effect of three separate incremental oral doses of famotidine on pentagastrin-stimulated gastric acid secretion in healthy volunteers.

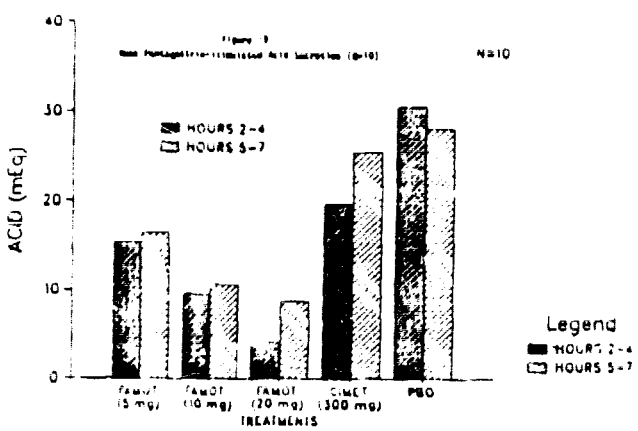
(2) Investigator: Richard W. McCallum, M.D., Yale University School of Medicine, New Haven, CT.

(3) Design of Study: double-blind, cross-over, placebo and active drug study in a 10 healthy volunteers. The procedure was similar to that of study No. 2 except that pentagastrin was infused intravenously at a rate of 1 mcg/kg/hr for two hours starting two hours after oral administration of famotidine 5, 10 or 20 mg, or cimetidine 300 mg or placebo. At the conclusion of the infusion, the subjects were permitted to become ambulatory for one hour after which a second continuous two-hour pentagastrin infusion was started. At the completion of this infusion, which was seven hours after administration of the test substance, the study day was completed.

(4) Results

(a) Safety: no drug-related adverse events were reported.

(b) Gastric secretion: a dose-related reduction in acid output following famotidine was observed after both pentagastrin-stimulated periods (figure 19). During the first period of stimulation acid output with famotidine 5, 10 and 20 mg was reduced 50%, 69% and 87% respectively, compared to 36% for cimetidine. During the second period of stimulation the respective degrees of inhibition were 41%, 62%, 69% and 7%.



(5) Conclusion: the results confirm those of the previous study in showing that famotidine inhibits pentagastrin-stimulated gastric acid output in a dose-related fashion for at least 7 hours after oral administration of the drug. In this study, moreover, the degree of inhibition with famotidine 5 mg was both greater and more prolonged than with cimetidine 300 mg.

d. Study No. 5

(1) Title: A double-blind, placebo controlled study to determine the effect of three separate incremental oral doses of famotidine on nocturnal and pentagastrin-stimulated gastric acid secretion in healthy volunteers.

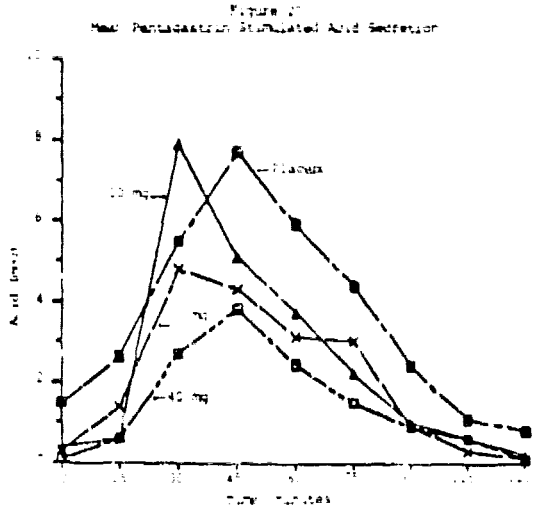
(2) Investigator: Sidney Cohen, M.D., and Ann Ouyang, M.D., Hospital of the University of Pennsylvania, Philadelphia, PA.

(3) Design of Study: the effects of single oral doses of famotidine 10, 20 and 40 mg were compared to placebo on pentagastrin-stimulated gastric acid secretion 9 1/2 hours after administration of the drug in 8 healthy volunteers in a double-blind, four-period cross-over study with a washout interval of 72 hours separating the treatments. The medication or placebo was self-administered at midnight. Pentagastrin 6 ug/kg was given subcutaneously 9 1/2 hours after ingestion of the drug; gastric secretion was determined for two hours thereafter.

(4) Results

(a) Safety: the only adverse experiences were those attributable to administration of pentagastrin.

(b) Gastric secretion (figure 20): during the first hour of pentagastrin stimulation there were statistically significant reductions of gastric acid output with famotidine 20 mg and 40 mg compared to placebo; during the second hour significant reduction of acid output occurred with all 3 doses of famotidine.

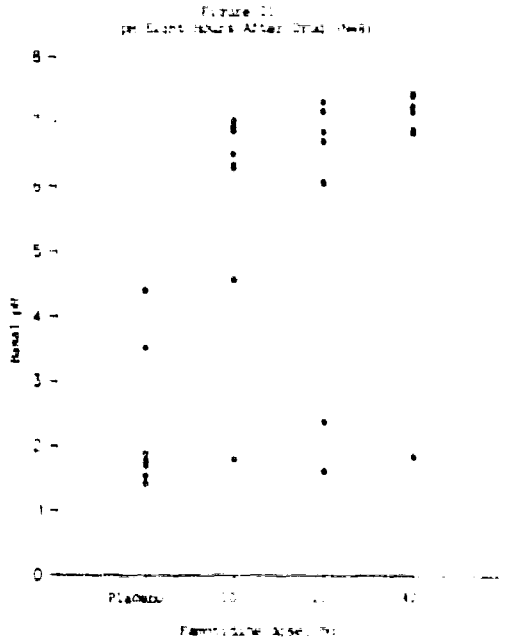


(5) Conclusion: Famotidine in single oral doses of 10, 20 and 40 mg inhibits pentagastrin stimulated volume and acidity of gastric secretion in a dose-related manner for a period of more than 11 hours.

e. Summary of studies on pentagastrin-stimulated secretion: famotidine in the proposed daily therapeutic doses (40 mg h.s. for short-term treatment of peptic ulcer, 20 mg h.s. for prevention of recurrence) inhibits acid secretion stimulated by pentagastrin administered by continuous IV, intramuscular or subcutaneous injection. The inhibition amounts to 60-70% compared to placebo, and lasts for up to 12 hours in some cases. A single oral dose of 5 mg has approximately the same inhibitory effect as a dose of 300 mg of cimetidine.

2. Nocturnal secretion

a. Study No. 5: the protocol was as reviewed above under IICld. The pH of nocturnal gastric secretion was elevated (figure 21) by single oral doses of famotidine 10, 20 and 40 mg for at least 8 hours. The pH values were above 6 in only 1 of the 8 subjects on placebo contrasted with 5 on famotidine. With the 40 mg dose the pH in all 8 subjects was above 7.0.



b. Study No. 7

(1) Title: A double-blind, placebo-controlled study to determine the effects of four oral dose levels of famotidine at the beginning and end of a 5-day dosing regimen on nocturnal and food stimulated acid secretion in volunteers who are hyper-secretors.

(2) Investigator: Jerome Ryan, M.D., Clinical Research Center, Inc., New Orleans, LA.

(3) Design of Study: the study was divided into three parts:

Part I evaluated nocturnal and food-stimulated acid secretion on the first and fifth day when doses of famotidine 5, 10, 20 and 40 mg and placebo were administered to 4 healthy volunteers at 9:00 PM each evening for 5 days. Each treatment period was separated by a 5 day interval. The study was discontinued when it became apparent that an effective dose had not been identified with the dosage regimens evaluated. Other dosage regimens were then explored in an open-label pilot study.

Part II evaluated the effects on nocturnal and meal-stimulated acid secretion over a 22-hour interval after administration of famotidine 40 or 80 mg or placebo at 7:00 AM in an open-label design to 2 healthy volunteers. Each treatment period was separated by an interval of 5 days.

Part III evaluated the effects on nocturnal and meal stimulated acid secretions over a 22-hour interval with dosage regimens of famotidine 10 mg b.i.d., 20 mg b.i.d., 80 mg at 9:00 PM or placebo in an open-label design to 3 healthy volunteers. Each treatment period was separated by an interval of 5 days. Volunteers were acceptable for the study on the basis of a basal secretory rate greater than 5 mEq/h.

(4) Results: nocturnal acid output measured from 12 midnight to 7:00 AM after a dose of drug at 9:00 PM was inhibited by about 90% by both a 40 and 80 mg dose of famotidine.

(5) Conclusion: effective inhibition of nocturnal acid secretion can be achieved with a single oral dose of famotidine 40 mg h.s. The effect on food-stimulated secretion will be discussed under that heading.

c. Study No. 51

(1) Title: A double-blind, placebo-controlled, randomized 3-way cross-over study in ambulatory duodenal ulcer patients in remission to evaluate the effect of famotidine on 24 hour intragastric pH profile and concurrent gastrin values.

(2) Investigator: J. Lacey Smith, M.D., Baylor College of Medicine, Houston, TX.

(3) Design of Study: duodenal ulcer patients in remission with a basal acid secretion greater than 5 mEq/h were assigned randomly to receive either placebo at 9:00 AM and 9:00 PM, famotidine 20 mg at 9:00 AM and 9:00 PM or placebo at 9:00 AM and famotidine 40 mg at 9:00 PM. Study day 7 of each treatment period was designated as monitoring day during which the 24 hour intragastric profile was monitored continuously and blood samples collected for measurement of serum gastrin. On all monitoring days the patients were given a choice of foods from a menu providing for the same intake of xanthine-containing foods and beverages. Meal times were 8:30 AM, 12 M and 5:00 pm. Four subjects completed the study.

(4) Results

(a) Safety: no drug-related adverse events were reported.

(b) Nocturnal acidity (table 2): the median and ranges of pH measured from 1:00 AM to 9:00 AM were placebo 1.38 (1.20-2.38), famotidine 40 mg at 9:00 PM 5.88 (3.90-6.05) and famotidine 20 mg at 9:00 AM and 9:00 PM 5.53 (3.92-6.97).

TABLE 2

Effect of famotidine on nocturnal acidity. Famotidine or placebo given orally at 9:00 PM. Mean intragastric pH measurements, 1:00 AM - 9

Patient	Famotidine 40 mg	Famotidine 20 mg	Placebo
1	5.05	6.97	1.38
2	3.92	4.94	1.20
3	5.88	3.92	2.38
5	5.95	6.11	1.38
Median	5.88	5.53	1.38
Range	3.90-6.05	3.92-6.97	1.20-2.38

(c) Food stimulated secretion is discussed below under IIC3a.

(5) Conclusion: in duodenal ulcer patients in remission, the pH of nocturnal gastric secretion was significantly higher in patients receiving famotidine than in those receiving placebo.

d. Summary of studies on nocturnal secretion: the proposed therapeutic doses of famotidine (40 h.s. for short-term treatment, 20 h.s. for prevention of recurrence) reduce nocturnal acid production by 85-95% and increase intragastric pH to as high as 4 to 7 compared to placebo levels up to 2.4.

3. Food-stimulated secretion

a. Study No. 7: this is the study described above (IIC2b) in which the effect on nocturnal secretion was reviewed.

(1) Results

(a) Safety: no serious adverse reactions attributable to famotidine were reported.

(b) Acidity: a significant increase in the pH following breakfast was observed as a carryover of the effect of the 20 mg b.i.d. and 40 mg h.s. doses compared to placebo (table 3). Neither the previous h.s. dose of 40 mg nor the dose of 20 mg at 9:00 AM had any effect on the pH following the evening meal.

TABLE 3

Effect of famotidine on acidity of food-stimulated gastric secretion

Patient	Mean intragastric pH 9:00 AM - 5:00 PM			5:00 PM - 9:00 AM		
	40 mg HS	20 mg BID	Placebo	40 mg HS	20 mg BID	Placebo
1	3.32	3.35	1.99	1.47	1.75	1.63
2	2.82	3.08	2.07	2.36	1.77	1.29
3	2.21	2.78	1.99	1.42	2.34	1.78
5	2.80	3.20	1.96	1.54	2.11	1.97
Median	2.81	3.14	1.99	1.51	1.94	1.88
Range	2.21-3.32	2.78-3.35	1.96-2.07	1.42-2.36	1.75-2.34	1.29-1.97

(c) Conclusion: a single h.s. dose of famotidine 20 or 40 mg has a moderate inhibitory effect on the gastric secretory response to breakfast on the following morning, but no effect on meals later in the day.

b. Study No. 51: the procedure and the effect on nocturnal secretion were reviewed above under IIC2c.

(1) Results

(a) Safety: the only clinical adverse experience occurred in a patient receiving placebo. The same subject also had an increase in band cells. One subject receiving famotidine 40 mg h.s. experienced transient pyuria, not considered drug-related.

(b) Effect on pH of digestive secretions: the mean pH measurements for each volunteer over the 9:00 AM to 5:00 PM interval were higher during administration of famotidine than during placebo, but the data were insufficient for statistical analysis.

c. Summary of studies on food stimulated secretion: insufficient data are available to permit conclusions regarding the effects of famotidine on food stimulated secretion in duodenal ulcer patients in remission. In healthy volunteers doses of 20 and 40 mg h.s. show a carry-over inhibitory effect on breakfast-stimulated acid output.

4. Gastric emptying and pancreatic secretion

a. Study No. 61

(1) Title of study: An open-label study to evaluate the effect of treatment with famotidine on gastric emptying and pancreatic exocrine secretion in healthy volunteers.

(2) Investigator: Richard Redinger, M.D., University of Louisville, Louisville, KY.

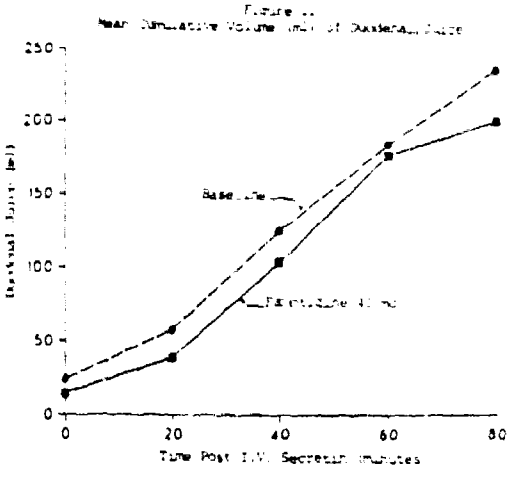
(3) Design of study: in 6 healthy male volunteers receiving famotidine 40 mg b.i.d for 7 days, labeled chicken pate in beef stew was used to measure the gastric emptying time of a solid meal, and pancreatic exocrine function was assessed by measuring volume, bicarbonate and amylase after intravenous secretin, before and after 7 days of treatment.

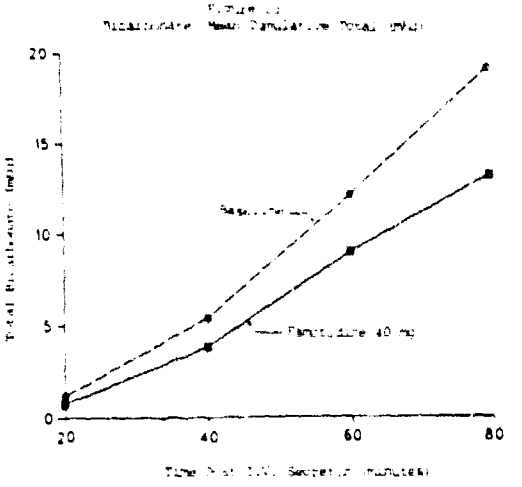
(4) Results

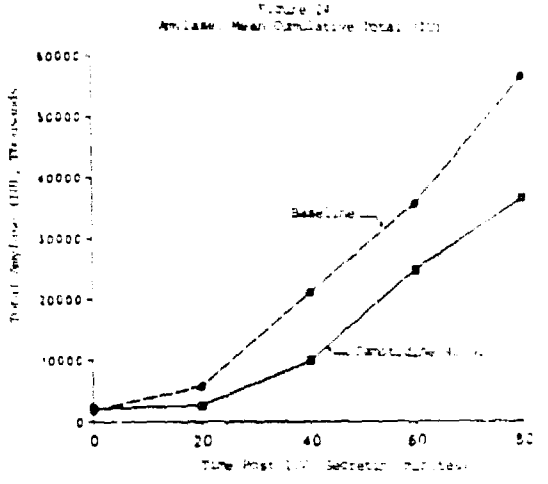
(a) Safety: No clinical adverse experiences or clinically important changes in laboratory parameters were observed.

(b) Gastric emptying: famotidine had no significant effect on gastric emptying.

(c) Pancreatic exocrine function: mean volume of secretion (figure 22) was not affected by famotidine; there was a trend towards a reduction in the output of bicarbonate (figure 23) and amylase (figure 24) but the differences were not significant.







(d) Conclusion: on the basis of the limited amount of data available from this one study there appears to be no significant effect of famotidine on gastric emptying or pancreatic exocrine secretion.

(e) Comment: the trend toward reduction of volume and especially of bicarbonate output after administration of famotidine may indicate a real effect. The less acid reaching the upper intestine, the less release of secretin and the less stimulus to these functions of the pancreas. This possibility could be better evaluated by determining the effect of famotidine on the basal secretions of the pancreas.

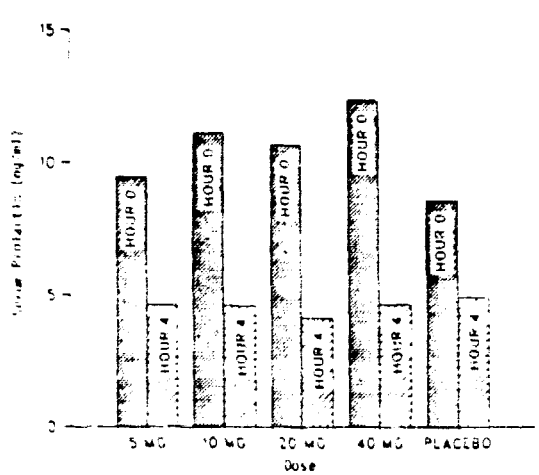
5. Summary of effects on gastric and pancreatic function: famotidine suppressed basal, food-stimulated nocturnal and pentagastrin stimulated volume and acidity of gastric secretion in a dose-related manner. The dose recommended for short-term treatment of peptic ulcer (40 mg h.s.) inhibited nocturnal secretion almost completely and had a significant carry-over effect on the acid response to a breakfast meal or an injection of pentagastrin secretion on the following morning. Pepsin concentration was not affected, but pepsin output was reduced in consequence of the reduction in volume of secretion. Famotidine had no effect on the rate of gastric emptying of a meal, nor, apparently, on secretin-stimulated pancreatic secretion.

D. Hormonal effects

1. Study No. 1: the protocol was described under "Human tolerance", (IIA2).

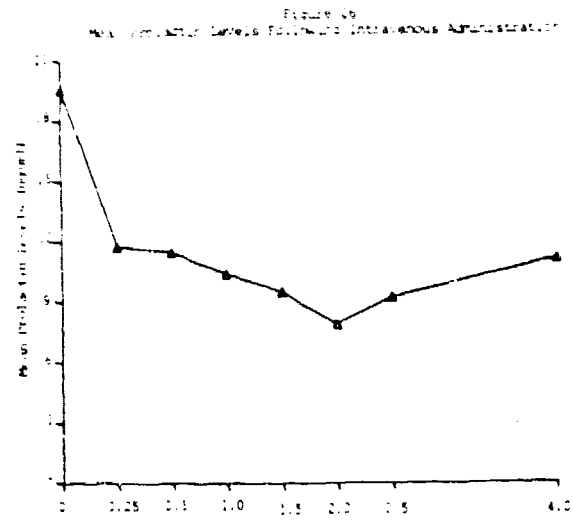
Effect on serum prolactin (figure 25): mean prolactin levels with all drug doses were higher at 0 hour than with placebo; these differences were thought to be attributable to the inherent variations of measurement. Four hours after dosing, significant mean decreases from 0 hour were observed for all treatments, probably reflecting diurnal variation.

Figure25
Mean Serum Prolactin 0-4 Hours Post-Dose (N=15)



2. Study No. 42: the protocol was reviewed under "Human Tolerance" (IIA2).

Effect on secretion of prolactin (figure 26): prolactin levels assessed over a period of 4 hours following intravenous administration of famotidine 20 mg were significantly lower than the pre-drug levels. The sponsor speculates that this might be because the baseline blood samples were obtained immediately after the subjects had stopped being ambulatory, whereas the post-drug samples were obtained while the subjects had been recumbent for some time. Also, the known diurnal variation in serum prolactin levels may have been a factor. At any rate, famotidine 20 mg administered intravenously did not stimulate prolactin secretion.



3. Study No. 31

a. Title of study: A double-blind, dose-ranging study to evaluate the effects on healing of active duodenal ulcer, famotidine compared to placebo.

b. Investigator: Ram K. Shrivastava, M.D., New York, New York.

c. Design of study: an addendum was made to this study to include measurement of selected hormones. Blood samples were taken at baseline and at the end of the short-term treatment of duodenal ulcer for determination of prolactin, FSH and LH, gastrin, and, in males, testosterone.

d. Results: some or all of the parameters were tested in up to 10 patients. Minor changes, not clinically important, were recorded, suggesting that famotidine has no effect on the hormones measured.

e. Conclusion: in this limited number of subjects, there was no apparent drug-related effect on hormone levels.

4. Summary of hormonal affects: famotidine did not stimulate the release of prolactin, FSH, LH or testosterone. Since there were no comparative studies with other H_2-blockers, the significance of these findings is questionable. An inhibitory effect of famotidine on prolactin secretion is not ruled out by the data submitted.

E. Drug interactions

1. Study No. 48

a. Title of study: An open label, randomized, 2-way, cross-over study to assess the e fect of famotidine and of cimetidine on the disposition of intravenous theophylline.

b. Investigator: Roger L. Williams, M.D., University of California, San Francisco, CA.

c. Design of study: an open, randomized, 2-way cross-over study in healthy volunteers to determine the effect of multiple oral doses of famotidine and cimetidine on the pharmacokinetics of intravenous theophylline as measured by plasma concentrations and urinary recovery.

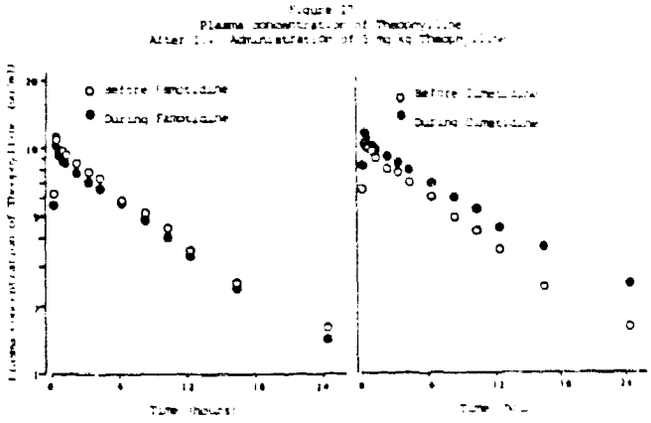
The pharmacokinetics of famotidine after single and multiple doses were also examined. The study was carried out in 10 healthy volunteers, 5 of each sex, ages 21-32, mean 24.5 years. Each study period was of 9 days duration and divided into 3 parts. Part 1 was a baseline segment consisting of the initial 2 days in which aminophylline (85% theophylline) 5 mg/kg was administered IV and plasma and urine collected to establish

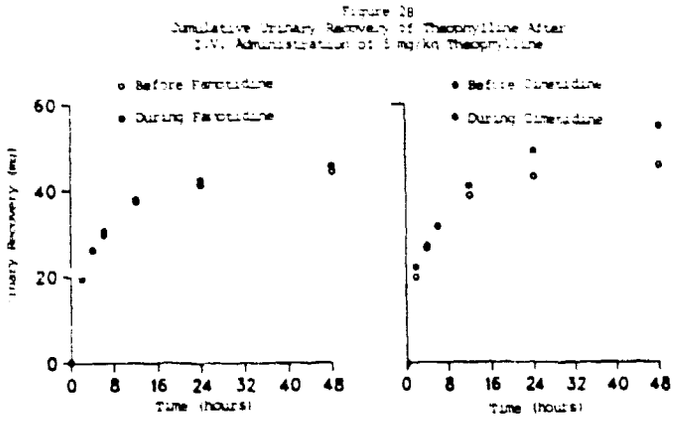
baseline concentrations of theophylline. Part 2 was a 1-day no-treatment washout segment. Part 3 was a drug treatment segment in which either famotidine 40 mg b.i.d. or cimetidine 300 mg q.i.d. was administered for 3 days and plasma and urine collected to establish single-dose and repeat-dose plasma concentrations of famotidine but not cimetidine. On the fourth day, aminophylline was given concomitantly with famotidine or cimetidine. Plasma and urine were collected for both drug groups for 48 hours and the findings compared with the baseline theophylline period. A minimum 7 day washout period separated the study periods. Adverse reactions were monitored throughout.

d. Results:

(1) Safety: no adverse clinical or laboratory events attributable to famotidine or cimetidine were reported.

(2) Disposition of theophylline: total body clearance of theophylline was unchanged by famotidine (58 vs 61 ml/min), but was significantly decreased by cimetidine (58 vs 40 ml/min), p 0.01. The half-life of theophylline remained constant during treatment with famotidine, but was significantly prolonged (9.3 to 12.2 h), p 0.05, with cimetidine. Plasma concentration (figure 27) and urinary excretion (figure 28) of theophylline remained unchanged during treatment with famotidine, but plasma concentration was increased and urinary recovery prolonged during treatment with cimetidine.





e. Conclusion: cimetidine in therapeutic dosage, but not famotidine in higher than anticipated therapeutic dosage, decreased the metabolic elimination of theophylline.

2. Study No. 53

a. Title of study: Effect of famotidine on the anticoagulant action of sodium warfarin in healthy volunteers.

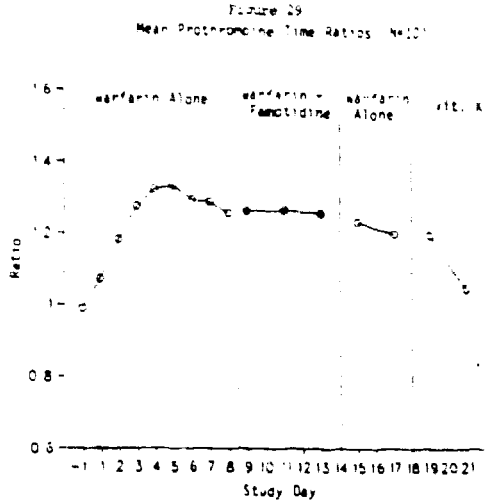
b. Investigator: Jerome R. Ryan, M.D., Clinical Research Center, New Orleans, LA.

c. Design of study: 10 healthy male subjects participated. During Period I the subjects received a single-oral dose of sodium warfarin in the evening; prothrombin times (PTs) were determined in the morning. The dose of sodium warfarin was adjusted by the investigator so that the subjects were sub-therapeutically anti-coagulated, defined as a PT which was just a few seconds longer than the subject's baseline (a maximum of 2.5 x control). The subject was maintained on this dosage to insure that a steady state had been achieved, defined as PTs on 3 consecutive days within 15% of each other. During Period II the subjects received famotidine 40 mg orally morning and evening for 4.5 days, the last dose having been administered on the morning of the 5th day; the maintenance dose of sodium warfarin was continued once a day in the evening for 5 days. During Period III the subjects received their maintenance dose of sodium warfarin once a day in the evening for 5 days followed by a brief washout period during which no drug was administered. At the beginning of the washout period, subjects received a single 5 mg dose of vitamin K. The washout period lasted until the subject's PT value was within one second of the baseline. Throughout the investigation blood samples for determination for PTs were collected at intervals appropriate to the purpose of the investigation.

d. Results

(1) Safety: five subjects reported clinical adverse experiences; one (watery stool with gas) was considered possibly drug-related. The symptoms were in no instance severe and all resolved without residual effects. No subjects were discontinued because of adverse experiences. One subject had an elevation of SGPT to 71 units (ULN 45) at the end of the study; the subject was lost to follow-up.

(2) Effect on prothrombin time (figure 29): famotidine did not affect the prothrombin time in normal volunteers receiving warfarin (range 2-10 mg/day) plus famotidine 40 mg orally daily for 4.5 days.



e. Conclusion: repeated administration of famotidine 40 mg b.i.d. for 4.5 days had no effect on the anticoagulant action of the sodium warfarin.

3. Study No. 55

a. Title of study: An open label, randomized, 2-way cross-over study to assess the effect of famotidine and of cimetidine on the disposition of oral phenytoin and on hepatic blood flow.

b. Investigator: Roger L. Williams, M.D., Drug Studies Unit, University of California, San Francisco, CA.

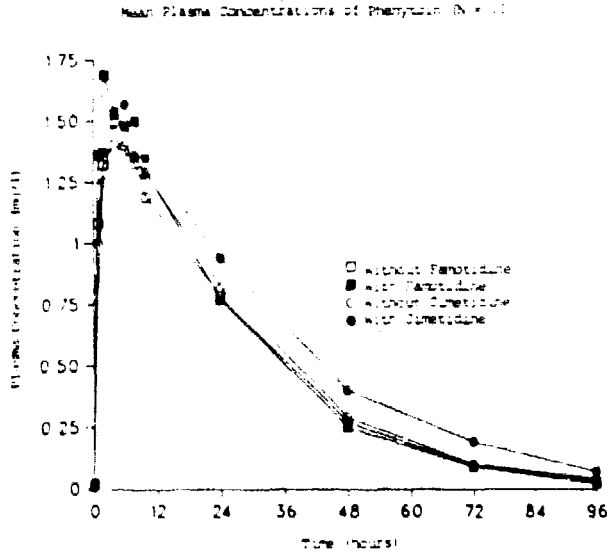
c. Design of Study: an open-label, randomized two-way cross-over study in 10 healthy volunteers, 8 men and 2 women ranging in ages from 20 to 47 years with a mean of 30.6 years, to examine the effects of repeated doses of cimetidine and of famotidine on the plasma kinetics of phenytoin given as a single oral dose and on the hepatic blood flow determined by the kinetics of indocyanine green (ICG) given intravenously. Part 1 of the study was a baseline segment consisting of 5 days in which oral phenytoin 100 mg and intravenous ICG 0.5 mg/kg were given on the morning of day 1 of the study. Blood and urine were collected for 96 hours to the morning of day 5. Part 2 was an 8-day drug-treatment period during which either famotidine 40 mg h.s. or cimetidine 300 mg q.i.d. were administered for 7 days from day 6 through day 12. Single doses of phenytoin 100 mg p.o. and ICG 0.5 mg/kg IV were given on the 3rd day of this period, i.e., day 9. Blood and urine samples were collected from the start of the phenytoin-ICG administration on study day 9 for 96 hours to the morning of study day 13. A minimum 14-day washout interval separated the 2 cross-over 13-day periods of the study. Phenytoin was given as Dilantin Capsules 100 mg p.o., ICG as a 10 second intravenous bolus.

d. Results:

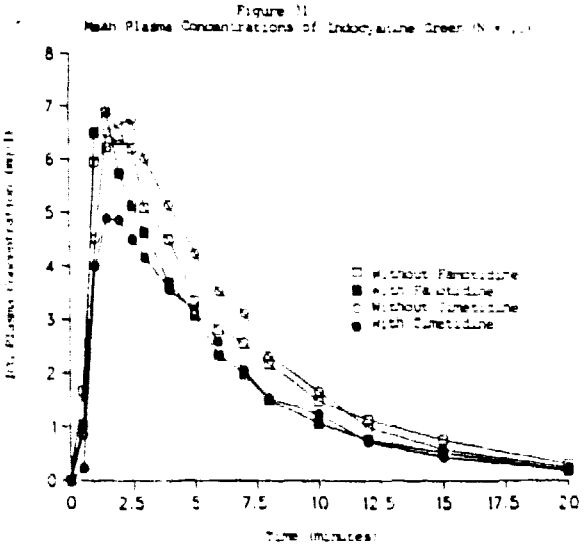
(1) Safety: no clinical or laboratory adverse events were reported.

(2) Pharmacokinetic observations

(a) Disposition of phenytoin: plasma concentrations of phenytoin were increased by concurrent administration of cimetidine but not famotidine (figure 30).



(b) Hepatic blood flow: neither drug had a significant effect on hepatic blood flow as determined by clearance of ICG (figure 31).



e. Conclusion: in contrast to cimetidine, famotidine does not interfere with the biological disposition of phenytoin. Neither drug appears to affect hepatic blood flow.

4. Study No. 58

a. Title of study: An open label, randomized 3-way cross-over study to assess the effects of famotidine, cimetidine and no-drug treatment on the disposition of intravenous diazepam.

b. Investigators: Miguel A. Zinny, M.D., Medical and Technical Research Associates, Needham, MA, and David A. Greenblatt, M.D., Division of Clinical Pharmacology, Tufts-New England Medical Center, Boston, MA.

c. Design of study: open, randomized, 3-way cross-over study in 13 healthy male volunteers to determine the effect of famotidine and cimetidine on the pharmacokinetics of diazepam. Each of 3 study periods lasted for 8 days. On day 2 of each period, diazepam 10 mg was given as a single intravenous infusion over 15 to 30 seconds at approximately 8 am, following which blood samples were drawn at intervals up to 168 hours. The minimum washout interval between study periods was 3 weeks. Co-administration of the test drugs began on day 1 and consisted of either famotidine 40 mg b.i.d. or cimetidine 300 mg q.i.d. for 8 days. In the other segment, no drug treatment was given in connection with the injection of diazepam.

d. Results

(1) Safety: of the 13 volunteers enrolled, one was discontinued because of abnormal liver function findings pre-study; this volunteer was replaced by another who, however, was lost to follow-up after completing the first study period (cimetidine co-administration). The remaining 11 volunteers completed the 3 study periods. The safety data from this study are combined with safety data from a previous protocol designated Study No. 56, which was the same protocol but was not suitable for analysis of effectiveness because a period of no drug treatment had not been included. Three of the subjects participating in study no. 56 had mild elevations of SGPT during both the famotidine and cimetidine periods; 4 of the subjects in protocol 58 also had mild elevations of SGPT or SGOT during both drug periods and 2 of them also had elevated SGPTs during no drug treatment. Clinical adverse experiences occurred in 2 patients receiving cimetidine but were very unlikely to be drug-related. No other adverse events were reported.

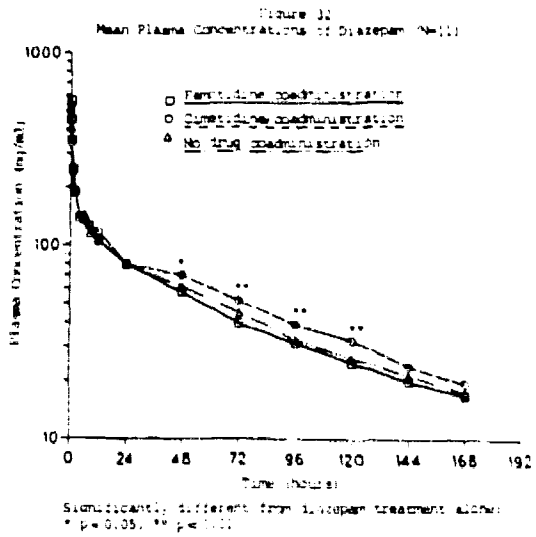
(2) Pharmacokinetics: co-administration of neither famotidine nor cimetidine influenced V_1 (apparent volume of distribution in the central compartment) or V_d (total apparent volume of distribution) of diazepam (table 4). However, cimetidine co-administration significantly prolonged the apparent diazepam elimination $t_{1/2}$ (half-life), increased AUC (total area under the plasma concentration time curve), reduced total clearance and increased the AUC of desmethyldiazepam. None of these effects were observed with co-administration of famotidine. Mean plasma concentrations of diazepam and desmethyldiazepam associated with co-administration of the respective treatments (figures 32 and 33) show that with cimetidine, but not with famotidine, there was a statistically significantly higher plasma concentration of diazepam from 24 through 120 hours and of its metabolite from 96 through 168 hours.

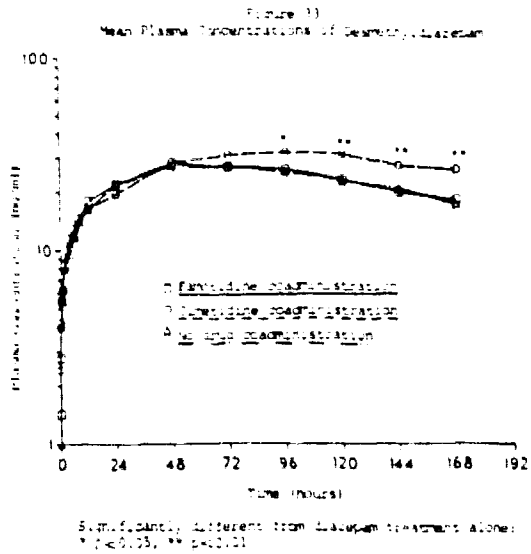
Table 4
Pharmacokinetic Parameters for Diazepam
and Desmethyldiazepam (mean ± SD)

PARAMETER	UNITS	TREATMENT COADMINISTRATION: FAMOTIDINE	CIMETIDINE	NO DRUG
Diazepam				
V_1	liters/kg	0.21 (0.06)	0.24 (0.05)	0.26 (0.14)
V_d	liters/kg	1.08 (0.36)	1.16 (0.37)	1.17 (0.38)
$t_{1/2}$	hr	52.6 (25.5)	72.2 ** (31.8)	54.2 (21.4d)
Total AUC	mg/ml x hr	9.45 (3.96)	11.76 ** (3.08)	9.78 (4.11)
Clearance	ml/min/kg	0.277 (0.117)	0.201** (0.054)	0.276 (0.136)
Desmethyldiazepam				
AUC Desmethyldiazepam	mg/ml x hr	3.93 (0.78)	4.58* (1.08)	3.84 (0.79)

*,** Significantly different from diazepam treatment alone, $p < 0.05$, $p < 0.01$, respectively

Note: No comparisons between RX-208 and cimetidine were performed.





e. Conclusion: treatment with famotidine 40 mg b.i.d., a dose higher than the recommended therapeutic dose in the treatment of peptic ulce· disease, does not alter the biological disposition of diazepam or its active metabolite desmethyldiazepam while cimetidine, in conventional therapeutic dosage, does. Thus, in contrast with what is observed with cimetidine, no problem is expected in the concurrent administration of famotidine with diazepam.

5. Study No. 690

a. Title of study: Famotidine and hepatic drug metabolism.

b. Investigators: Professor M. J. S. Langman and Dr. K. W. Somerville, Department of Therapeutics, Nottingham Medical School, Nottingham, England.

c. Design of study: open label design evaluating the effect of multiple doses of famotidine on the hepatic metabolism of 8 healthy volunteer subjects. Once during the week prior to the start of famotidine treatment and on day 7 following the morning dose of famotidine each subject received antipyrine 1 g orally, immediately following which the subjects also received ^{14}C-aminopyrine 2 microcuries as an intravenous bolus. Saliva and breath samples were obtained from each subject at specified intervals during the pre-treatment baseline and on day 7. Famotidine 40 mg was administered before breakfast and before the evening meal. Samples of saliva were assayed for antipyrine concentration as an index of plasma antipyrine concentration. $^{14}CO_2$ dpm was measured by liquid scintillation counter to indicate the hepatic demethylation of aminopyrine.

d. Results

(1) Safety: one of the 8 subjects experienced mild diarrhea throughout the 7 days on famotidine; this subsided after the investigation was completed. Two of the subjects experienced mild fatigue throughout the drug-taking phase of the investigation. One subject had a minor increase in SGPT at the end of treatment; the result of a repeat test 3 months later was normal.

(2) Hepatic drug metabolism: after 7 days of treatment with famotidine 40 mg b.i.d. the mean elimination half-life of antipyrine and aminopyrine decreased less than 10% from baseline.

e. Conclusions: the sponsor concludes, on the basis of a statistical analysis, that there is a 95% probability that the median increase from baseline levels in antipyrine half-life is less than 10% and an equal probability that the median increase in aminopyrine half-life is less than 25%.

f. Comment: in fact, one of the subjects showed an increase in the antipyrine half-life and 2 showed an increase in the aminopyrine half-life; consequently, it would appear valid to conclude that famotidine may, in some individuals, impair the oxidative metabolic functions of the liver.

6. Summary of results of studies on drug interactions: data submitted in this section are supported by a published paper (Staiger C et al, Arzneim Forsch 1984; 34:1041-1042) in concluding that famotidine does not affect oxidative metabolic functions of the liver. These observations are supported further in the results of studies showing absence of interaction of famotidine with diazepam, theophylline, phenytoin and warfarin. These data indicate that these drugs may be given without need for dosage adjustment in patients taking famotidine.

F. Ancillary studies

1. Study No. 12

a. A double-blind, dose-ranging study to evaluate the effects on healing of active duodenal ulcers with famotidine compared to placebo.

b. Investigator: Edward Cattau, Jr., M.D., National Naval Medical Center, Bethesda, MD.

c. Design of study: in the course of this clinical trial, samples of gastric secretions were obtained at the baseline endoscopy, at the end of the short-term study and at the end of 6 months (treatment was continued to evaluate prevention of recurrence). During endoscopy 5 ml of aspirate was collected in a sterile syringe for both qualitative and quantitative analysis of aerobic and anaerobic organisms.

d. Results: only 5 patients were evaluated, all during the short-term treatment period, and in only one patient was a change in gastric flora observed.

e. Conclusion: the data are insufficient to permit any conclusions regarding a possible famotidine-related effect on gastric flora.

III Clinical Trials

A. United States studies

1. Protocol No. 5006 (US multicenter trial)

a. Title of study: Famotidine in the short-term treatment of duodenal ulcer.

b. Design of the trial

(1) Admission criteria: patients with clinical symptoms of duodenal ulcer with an endoscopically demonstrated duodenal ulcer 0.5 to 2.5 cm in longest dimension.

(2) Exclusions

(a) Pyloric stenosis or peptic ulcer other than in the duodenal bulb
(b) Zollinger-Ellison syndrome
(c) Complications such as perforation or gross hemorrhage within 7 days
(d) Treatment with anticholinergics or H_2-blockers within the previous week
(e) Concomitant significant disease
(f) Lactation or child-bearing potential.

(3) Clinical observations: history of previous peptic ulcer disease, alcohol and smoking habits, physical examination, ECG, conventional clinical laboratory tests and upper endoscopy to confirm the presence of duodenal ulcer(s). Follow-up assessments of clinical symptoms were made and endoscopies performed at weeks 2, 4 and 8. Once ulcer healing was demonstrated at any of these intervals, the patients were eligible to be re-randomized into a 1 year maintenance study. Those whose ulcers had not healed at the end of 8 weeks were considered to have completed the study as a treatment failure. At each treatment visit the patients were given diary cards for daily recording of day and night pain, gastrointestinal symptoms, number of antacid tablets taken and any adverse experiences. The data from these diaries were reviewed at each visit. At the completion of the study the physical and laboratory examinations were repeated.

(4) Treatment schedules: patients were randomized to one of the following 4 dosage regimens.

(a) Famotidine 40 mg h.s. (placebo at 8:00 am, famotidine at 10:00 pm)

(b) Famotidine 20 mg b.i.d., 8:00 AM and 10:00 PM

(c) Famotidine 40 mg b.i.d., 8:00 AM and 10:00 PM

(d) Placebo at 8:00 AM and 10:00 PM

(5) Antacids: each patient received a bottle of antacid tablets to be taken only if additional symptomatic relief was required.

c. Evaluation criteria

(1) Endoscopy

(a) Normal: no ulcer present, complete epithelization of the ulcer crater, regardless of the persistence or emergence of duodenitis and/or erosions.
(b) Ulcer: incomplete epithelization of the ulcer.

(2) Pain: severity of day and night pain was recorded by the patient on a scale of 0 = none, 1 = mild, 2 = moderate and 3 = severe. The terms were not defined.

(3) Patients' assessments of global response to therapy were graded 0 = none, 1 = poor, 2 = fair and 3 = good and 4 = excellent, again without definition of the terms.

(4) Safety: adverse clinical and laboratory events were recorded and evaluated by the investigator as to severity, seriousness, relationship to study drug and outcome.

d. Statistical treatment: the analysis of effectiveness at each time point was done as an "end point" analysis, i.e., patients whose ulcers healed at weeks 2 or 4 actually completed the study per protocol and subsequently did not have data. The specific methods of analysis of the data are indicated in the tabulations of the results. Validity of the statistical methods applied by the sponsor in this and subsequent trials is the subject of a separate review of this NDA by FDA biometricians.

e. Investigators (table 5): all of the physicians participating in this clinical trial are well-qualified by training and experience to undertake studies of this type.

Table 5

Name/Study No	Affiliation	Location
Elliot Alpert, M.D./43	Methodist Hospital	Houston, Texas 77030
Robert N. Bishop, Jr., M.D./10	3266 N. Meridian Street	Indianapolis, IN 46208
James H. Butt III, M.D. 11	Veterans Administration Hospital	Columbia, MO 65212
James Campbell, M.D./22	University of Nebraska Med.Ctr.	Omaha, Nebraska 68105
Edward C. Cattau, Jr., M.D./12	National Naval Medical Center	Bethesda, Maryland 20014
William Erdel, M.D./16	St. Vincent's Hospital	Indianapolis, IN 46260
Norman Gitlin, M.D./13	Veterans Admin. Hospital	Fresno, CA 93703
Daniel Pelot, M.D./14	University of California	Irvine, CA 92717
Shanawaz Jaffer, M.D./19	Magan Medical Clinical Inc.	Covina, CA 91723
James H. Johnson, M.D./12	Watson Clinic	Lakeland, FLA 33801
R. Bruce Johnson, M.D. 15	Rees-Steely Medical Group	San Diego, CA 92101
James F. King, M.D.,'18	Gastroenterology Associates	Canton, Ohio 44708
Stephen M. Levine, M.D./35	1510 Brace Road	Cherry Hill, NJ 08034
Ross Madden, M.D./49	Medical Associates Clinic, P.C.	Dubuque, Iowa 52001
Arthur J. McCullough, Jr., M.D. 44	Metropolitan General Hospital	Cleveland, Ohio 44109
Frank Miao, M.D./24	Fullerton Internal Medicine Clinic	Fullerton, CA 92635
William A. Millhon, M.D. 23	3130 Olentangy River Road	Columbus, OH 43214
Richard Redinger, M.D. 25	University of Louisville	Louisville, KY 40202
Allen Rubin, M.D./21	5959 Harry Hines Blvd	Dallas, TX 75235
Ivan Rudolph, M.D. 26	Brachfeld Medical Associates	Willingboro, NJ 08046
Cesar Rudzki, M.D. 46	Washington Center for Clinical Studies	Washington, DC
Ram Shrivastava, M.D./31	Eastside Comprehensive Medical Services	New York, NY 10021
J. Lacey Smith, M.D./28	Veterans Admin. Medical Center	Houston, TX 77211
Joseph Spear, M.D. 27	6004 Ventnor Ave.	Ventnor City, NJ 08406
E.Clinton Texter,M.D./29	Univ. of Arkansas for Medical Sciences	Little Rock, AR 72205
Joycelyn Theard, M.D./45	San Antonio Center for Clinical Studies	San Antonio, TX 78212
Fred B. Thomas, M.D./09	Ohio State University	Columbus, OH 43210
Ronald Thune, M.D./50	West Side Clinic, S.C.	Green Bay, WI 54303
Jorge Valenzuela, M.D./38	U.S.C. Medical Center	Los Angeles, CA 90033
Stephen D. Ward, M.D./04	1245 Highland Ave.	Abington, PA 19001
Robert M. Griffin, M.D./30	Florida Center for Clinical Studies	St.Petersburg, FL 33701
Dominic Wong, M.D. 47	Henry Ford Hospital	Detroit, MI 48202
Herbert A. Yantes, M.D./57	Phila. Center for Clinical Studies	Philadelphia, PA 19152
Alvin M. Zfass, M.D. 32	Medical College of Virginia	Richmond, VA 23298

f. Results

(1) Comparability of treatment groups (table 6): the 4 treatment groups were comparable in all essential characteristics.

TABLE 6

Comparability of Treatment Groups, Number 1

	40 mg famotidine once daily	20 mg famotidine twice daily	40 mg placebo once daily	Pooled placebo
Age				
Mean	45.8	47.3	43.5	46.4
Sex				
Males	75 (78)	69 (78)	81 (81)	76 (79)
Females	21 (22)	20 (22)	19 (19)	41 (21)
Weight (lb.)	167.9	171.9	171.1	169.5
Smoking	58 (60)	52 (58)	57 (57)	55 (57)
Alcohol	18 (19)	12 (13)	14 (14)	13 (13)
Caffeine	56 (58)	59 (66)	62 (62)	54 (56)
Initial ulcer size (cm)[a]				
Mean	1.30	0.97	1.11	1.30
Number of ulcers				
One	79 (81)	73 (82)	80 (80)	82 (85)
Two or more	17 (18)	16 (18)	20 (20)	14 (15)
Age at first ulcer				
Mean	37.9	40.0	38.5	39.7
Duration of ulcer (yrs)				
Mean	7.7	6.7	7.9	6.7
Ulcer History				
None	30 (31)	42 (47)	34 (34)	26 (26)
Single	22 (23)	19 (21)	24 (24)	30 (30)
Multiple	44 (46)	28 (31)	41 (42)	44 (44)
Other pathology in esophagus	24 (25)	27 (30)	26 (26)	33 (33)
Other pathology in stomach	32 (33)	26 (29)	32 (32)	31 (31)
Other pathology in duodenum	63 (66)	50 (56)	67 (68)	63 (63)
Concomitant diseases				
Cardiovascular	7 (7)	9 (10)	11 (11)	7 (7)
Respiratory	4 (4)	4 (4)	6 (6)	3 (3)
Gastrointestinal	9 (9)	10 (11)	5 (5)	13 (13)
Musculoskeletal	6 (6)	10 (11)	6 (6)	2 (2)
Endocrine	5 (5)	2 (2)	5 (5)	8 (8)
Other	4 (4)	7 (8)	7 (7)	7 (7)

[a]For patients with more than one ulcer, this was the size of the largest ulcer. No significant differences were observed.

(2) Safety

(a) Vital signs (table 7): there was a statistically significant decrease in the mean pulse rate in patients receiving 40 mg b.i.d. and in the mean systolic blood pressure in patients receiving 40 mg h.s; these changes are not, however, of any clinical significance.

TABLE 7

Effect of Treatment on Vital Signs - Means

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE FROM BASELINE
Pulse rate (beats/min)	40 mg h.s.	94	75.9	74.5	-1.3
	20 mg b.i.d.	80	76.1	75.4	-0.7
	40 mg b.i.d.	95	76.8	73.9	-2.9 ** ##
	Placebo	97	76.1	76.1	0.0
Systolic BP (mmHg)	40 mg h.s.	96	122.4	119.5	-2.9*
	20 mg b.i.d.	87	123.5	124.8	1.3
	40 mg b.i.d.	95	123.1	123.5	0.4
	Placebo	97	125.0	123.0	-1.7
Diastolic BP (mmHg)	40 mg h.s.	96	77.3	75.9	-1.4
	20 mg b.i.d.	87	77.4	78.2	0.8
	40 mg b.i.d.	95	78.1	78.4	+0.3
	Placebo	97	77.6	78.0	0.4
Weight (lbs.)	40 mg h.s.	91	169.9	168.5	-1.4
	20 mg b.i.d.	83	171.9	172.1	0.2
	40 mg b.i.d.	91	170.1	170.1	+0
	Placebo	89	166.5	167.0	0.5

*,**,### = significant change from baseline, $p \leq .05$, $p \leq .01$, respectively.
#,##,### = significant difference from placebo, $p \leq .05$

(b) Laboratory adverse events: in patients on famotidine there were no serious abnormal laboratory values; no patient receiving famotidine was withdrawn because of an adverse laboratory event. The one patient with a laboratory finding considered serious was on placebo.

(c) Clinical adverse experiences: the percentage of patients with adverse signs/symptoms (table 8) regardless of drug-relationship was no greater with famotidine treatment (27%) than with placebo (39%) The incidence of adverse experiences in patients 60 years or older was not different from that in the general population.

TABLE 8

Number of Patients with Clinical Adverse Events [a]*

	Famotidine			
BODY SYSTEM	40 mg h.s. N = 96	20 mg b.i.d. N = 99	40 mg b.i.d. N = 99	PLACEBO N = 97
Central nervous system				
Dizziness	1	2 (2)	1	4 (4)
Fatigue	1	1	1	1
Headache	5	6 (6)	9 (9)	11 (11)
Insomnia	2	3 (3)	3	3 (3)
Nervousness	2	3 (3)	2 (2)	3 (3)
TOTAL	11	15 (15)	16 (16)	20 (20)
Cardiovascular (Thrombophlebitis)	2	1	2 (2)	4 (4)
Digestive				
Abdominal pain	1	1 (1)	2	2 (2)
Anorexia	1	1 (1)	1 (1)	1 (1)
Constipation	1	1 (1)	1	1
Diarrhea	4 (4)	3 (3)	1 (1)	5 (5)
Dyspepsia	1 (1)	2	1	2
Flatulence	1 (1)	1	2	2 (2)
GI hemorrhage	4 (4)	1	1	1 (1)
Nausea	2 (2)	1 (1)	1	3 (3)
TOTAL	17 (16)	11 (8)	9 (8)	14 (14)
Respiratory system				
Common cold	1	3 (3)	0	1
Cough	1	2 (2)	1	1 (1)
Pharyngeal Pain	0	2 (2)	0	1 (1)
TOTAL	2	7 (6)	1	3 (3)
Integumentary				
Hypersensitivity	0	0	2 (2)	0
TOTAL	23 (24)	30 (34)	23 (23)	39 (39)

*Adverse experiences with an incidence of at least 2% in at least one of the treatment groups are displayed in this table

A more meaningful analysis lists the patients withdrawn from treatment because of adverse signs/symptoms (table 9); here the incidence seems appreciable (2-3% on drug, 5% on placebo) but many of these adverse occurrences represent complications of the underlying peptic ulcer disease. In evaluating the possible drug-relationship of these occurrences I have chosen to classify the sponsor's "probably not" as "possibly yes". Even with this "strict construction" it is clear that in this clinical trial famotidine appears to be a relatively safe drug.

TABLE 9

Patients withdrawn because of Adverse Signs Symptoms

TREATMENT	ALOG	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	TOTAL POSSIBLY DRUG-RELATED
Famotidine 40 HS	1218	Gastric ulcer	Severe	Probably not[a]	
		Hematemesis	Severe	Probably not	
	1216	Herpes zoster	Severe	Probably not	
	1035	Acute hemorrhage	Severe	Def. not	
		Hematemesis	Severe	Def. not	
		Syncope	Severe	Def. not	
	1004	Acute hemorrhage	Moderate	Poss bly	3/96 3%
Famotidine 20 BID	1037	Gastric ulcer	Mild	Possibly	
	1039	Asthma	Severe	Probably not	
	1036	Chest pain	Moderate	Probably not	
		Nausea	Moderate	Probably not	
		Vomiting	Moderate	Probably not	3/84 3%
Famotidine 40 BID	1099	Grand mal seizures	Severe	Possibly	
	1094	Conjunctival injection	Mild	Probably	
		Orbital edema	Mild	Probably	2/99 2%
PLACEBO	1021	Vomiting	Severe	Def. not	
	1028	Chest pain	Moderate	Probably not	
	1031	Gastric ulcer	Mild	Possibly	
	1035	Headache	Mild	Possibly	
		Nausea	Mild	Possibly	
		Vomiting	Mild	Possibly	
	1019	Asthenia	Moderate	Possibly	
		Headache	Mild	Possibly	
		Abdominal swelling	Moderate	Possibly	
		Constipation	Moderate	Possibly	
	1035	Gastric ulcer	Mild	Possibly	5/100 5%

[a] Probably not = Possibly yes

(3) Effectiveness

(a) Number of patients evaluable: patients omitted from analysis of effectiveness (table 10) were remarkably few (22/384, 6%) considering the large number of patients entered in each treatment group. These non-cooperative patients or investigators (protocol violations, off drug) were identified early in the trial so that very few were lost after week 2. As might be expected, discontinuation because of ineffective therapy was highest in the placebo group (13%), but less expected was the high incidence (8%) of discontinuation because of adverse experiences.

Table 10
Number of Patients in Analysis of Results

	WEEK 2				WEEK 4				WEEK 8			
	Famotidine				Famotidine				Famotidine			
	40 HS	20 BID	40 BID	PBO	40 HS	20 BID	40 BID	PBO	40 HS	20 BID	40 BID	PBO
Total Entered	96	89	99	100	96	89	99	100	96	89	99	100
Patients with Incomplete Data												
Discontinued Adverse Experience	3	2	1	2	3	2	2	7	4	3	2	8
Discontinued Ineffective Therapy	0	1	1	6	1	1	1	10	1	1	1	13
Discontinued Other	3	3	3	4	5	4	3	10	5	4	8	10
Protocol Violations[b]	4	4	6	3	4	4	6	3	4	4	6	3
Off Drug[b]	2	0	0	0	3	1	0	0	3	1	0	0
No Treatment Data[c]	4	3	5	0	3	2	5	0	3	2	5	0
Total Included[a]												
Ulcer Healing	90	85	93	97	89	84	93	97	89	84	93	97
Day/Night Pain	86	82	85	97	86	82	88	97	86	82	97	86

[a] Patients who dropped out, were out of range, etc. had their last valid values carried forward to subsequent timepoints.
[b] Not included in per protocol ulcer healing and day/night pain analysis.
[c] Not included in per protocol day/night pain analysis.

(b) Incidence of healing: the sponsor tabulates the incidence of healing at weeks 2, 4 and 8; week 2 included endoscopies performed up to 18 days on treatment, week 4 up to 34 days and week 8 up to 65 days. The results (table 11) leave no doubt that all three doses of famotidine yield a similar incidence of healing and all are significantly more effective than placebo.

Table 11
Cumulative Number Healed/Number in Treatment Group (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=89	Famotidine 20 BID N=94	Famotidine 40 BID N=93	Placebo N=97
2 (Days 1-28)	28 (32)	32 (38)	31 (33)	16 (17)
4 (Days 19-34)	62 (70)	56 (67)	69 (74)	30 (31)
8 (Days 35-64)	74 (83)	69 (82)	75 (81)	44 (45)
Beyond Week 8 (Days 65-85)	75 (84)	69 (82)	76 (82)	44 (45)

At each time point, each of the famotidine treatment groups had a significantly higher healing rate than placebo, $p<.001$

Since, however, demonstration of healing after 34 days of treatment is manifestly not proof of healing within 4 weeks, I requested the sponsor to tabulate the incidence of healing by actual weeks. This tabulation (table 12) shows that if the first follow-up endoscopy is performed at 5 weeks, a significantly smaller percentage of patents will require further treatment and an additional endoscopy. With the recommended dose (40 mg h.s.) the incidence of healing at 5 weeks was 70% compared to 53% at 4 weeks; with 40 mg b.i.d., the incidence of healing at 5 weeks was 75% compared to 54% at 4 weeks.

TABLE 12

Cumulative Number Healed (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=89	Famotidine 20 BID N=84	Famotidine 40 BID N=93	Placebo N=97
Week 1 (Days 2-8)*	0 (0)	0 (0)	0 (0)	0 (0)
Week 2 (Days 9-15)	21 (24)	25 (30)	20 (22)	8 (8)
Week 3 (Days 16-22)	31 (35)	35 (42)	32 (34)	16 (16)
Week 4 (Days 23-29)	47 (53)	49 (58)	50 (54)	24 (25)
Week 5 (Days 30-36)	62 (70)	57 (68)	70 (75)	30 (31)
Week 6 (Days 37-43)	62 (70)	59 (70)	70 (75)	30 (31)
Week 7 (Days 44-50)	63 (71)	59 (70)	70 (75)	30 (31)
Week 8 (Days 51-57)	70 (79)	62 (74)	72 (77)	39 (40)

* Day 1 was the day of the baseline evaluation. Patients started taking drug at bedtime on day 1. All weekly day ranges start with day 2.

Among the 5 investigators who contributed at least 20 patients there was generally not much treatment-by-investigator interaction (table 13) except as regards placebo incidence of healing which varied from 10 to 60% at 4 weeks, 33-80% at 8 weeks. This is not a novel observation.

TABLE 13

Number (%) Healing Reported by Investigators with at Least 20 Patients — Number (%) Healed

Inv.	Famotidine 40 HS N	wk 2	wk 4	wk 8	Famotidine 20 BID N	wk 2	wk 4	wk 8	Famotidine 40 BID N	wk 2	wk 4	wk 8	Placebo N	wk 2	wk 4	wk 8
1	6	0 (0)	1 (17)	6 (100)	4	2 (50)	3 (75)	3 (75)	5	2 (40)	4 (80)	5 (100)	5	1 (20)	3 (60)	4 (80)
2	7	2 (29)	5 (71)	5 (71)	7	2 (29)	3 (43)	5 (71)	6	3 (50)	5 (83)	5 (83)	7	2 (29)	3 (43)	3 (43)
3	10	3 (30)	5 (50)	5 (50)	8	4 (50)	5 (63)	6 (75)	9	0 (0)	8 (89)	9 (100)	10	1 (10)	1 (10)	4 (40)
4	8	4 (50)	8 (100)	8 (100)	9	3 (33)	5 (56)	5 (56)	6	1 (17)	3 (50)	3 (50)	9	1 (11)	2 (22)	4 (44)
5	7	4 (57)	6 (86)	7 (100)	8	3 (38)	7 (88)	8 (100)	7	5 (71)	7 (100)	7 (100)	9	3 (33)	3 (33)	3 (33)
SUBTOTAL	38	13 (34)	25 (66)	31 (82)	36	14 (39)	23 (64)	27 (75)	33	11 (33)	27 (82)	29 (88)	40	8 (20)	12 (30)	18 (45)
*Pool	51	15 (29)	37 (73)	43 (84)	48	18 (38)	33 (69)	42 (88)	60	20 (33)	42 (70)	46 (77)	57	8 (14)	18 (32)	26 (46)
TOTAL	89	28 (32)	62 (70)	74 (83)	84	32 (38)	56 (67)	69 (82)	93	31 (33)	69 (74)	75 (81)	97	16 (16)	30 (31)	44 (45)

*All Other Investigators Combined

(c) Effect of treatment on duodenitis/erosions: duodenitis and/or erosions co-existed with the duodenal ulcers in 201/363 (55%) of patients in whom such information was available at the pre-treatment endoscopy. Some observers consider the presence of duodenitis and/or erosions part of the spectrum of peptic ulcer disease. It is therefore of interest to evaluate the effect of treatment on these lesions and any effect their presence may have on ulcer healing (table 14). Among patients in whom the endoscopic records included reports of the presence or absence of duodenitis and/or erosions both before and after treatment in the same patients, the post-treatment incidence of duodenitis and/or erosions in patients in whom these lesions were not present pre-treatment was 24/78 (31%) on famotidine, 11/32 (34%) on placebo; the emergence of these lesions during treatment had no effect on healing of the ulcers. In patients in whom duodenitis and/or erosions were present pre-treatment, such lesions persisted in 84/146 (58%) on drug, 38/54 (72%) on placebo; the persistence of these lesions had no effect on the healing of the ulcers.

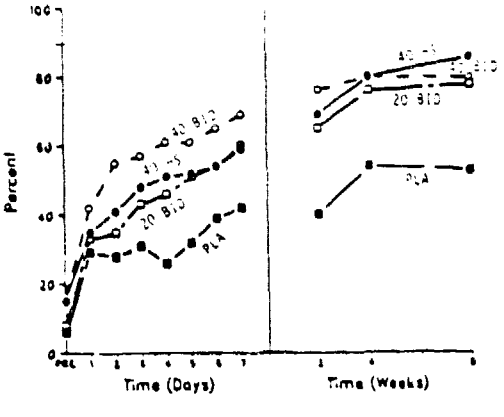
TABLE 14

Effect of Treatment on Incidence of Duodenitis/erosions and relation to healing of ulcer

Duodenitis/erosions pre-treatment	Duodenitis and/or erosions post-treatment and percent ulcers healed: FAMOTIDINE N	%	ulcer healed	%	TOTAL N	%	ulcer healed	%	PLACEBO N	%	ulcer healed	%
None	11/74	46	11/11	100	6/28	21	5/6	83	7/26	27	7/7	100	24/78	31	23/24	96	11/32	34	4/11	36
Duodenitis/erosions	32/63	51	26/32	81	26/43	60	21/26	81	26/51	51	23/26	88	84/146	58	70/84	83	39/54	72	19/39	49
TOTAL	43/137	49	37/43	86	32/71	45	26/32	81	33/77	43	30/33	91	108/225	48	93/108	86	50/86	58	23/50	46

(d) Relief of pain: the proportion of patients relieved of day pain was higher at all time points from the 3rd day onward through 8 weeks with all doses of famotidine than with placebo (figure 34). The proportion of patients relieved of night pain at the end of the first week was higher with the 40 mg h.s. and 40 mg b.i.d. doses than with 20 mg b.i.d. or placebo; from the second week onward, proportionately more patients receiving any dose of famotidine were relieved of night pain than were those receiving placebo (figure 35). The median number of days to relief of pain was significantly fewer with all doses of famotidine than with placebo (table 15).

Figure 34
Percentage of Patients with No Day Pain



Percentage of Patients with No Night Pain
Figure 35
Percentage of Patients with No Night Pain

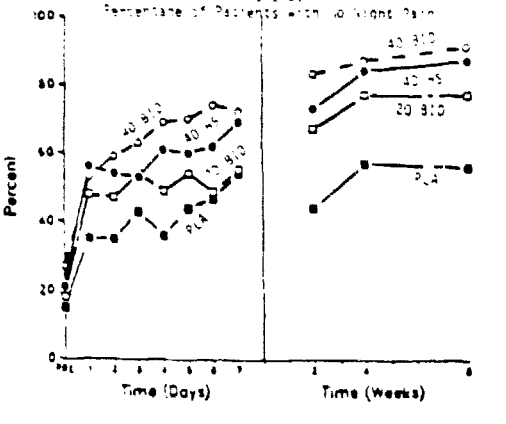


Table 15
Incidence, and Median Time to, Relief of Pain (Days)

		FAMOTIDINE 40 HS (n = 89)	20 BID (n = 84)	40 BID (n = 93)	PLACEBO (n = 97)
Day Pain					
Incidence (%)		76 (85)	77 (92)	78 (84)	91 (94)
Baseline =	None[a]	10 (n = 13)	1 (n = 7)	13 (n = 15)	22 (n = 6)
	Mild	6 (n = 23)	13 (n = 18)	4 (n = 25)	64 (n = 29)
	Moderate	14 (n = 35)	14 (n = 36)	10 (n = 39)	55 (n = 37)
	Severe	12 (n = 18)	20 (n = 23)	10.5 (n = 14)	27 (n = 25)
	Total	11 (n = 89)	14.5 (n = 84)	9 (n = 93)	54 (n = 97)
Night Pain					
Incidence (%)		76 (85)	60 (81)	65 (70)	82 (85)
Baseline =	None[a]	6.5 (n = 13)	6.5 (n = 16)	2 (n = 27)	11 (n = 15)
	Mild	10 (n = 21)	16 (n = 16)	2 (n = 17)	34.5 (n = 20)
	Moderate	9 (n = 33)	21 (n = 29)	9.5 (n = 28)	64 (n = 33)
	Severe	19 (n = 15)	11 (n = 23)	22 (n = 20)	54 (n = 29)
	Total	10 (n = 89)	14.5 (n = 84)	5.5 (n = 92)	52 (n = 97)

[a] Some patients had no pain at baseline but had pain at one or more subsequent timepoints. A significant within-group change from baseline was observed for each treatment group, $p<.01$. For both relief of Day Pain and relief of Night Pain, each of the famotidine groups were significantly better than placebo, $p < .001$.

(e) Antacid consumption: throughout most of the 8 weeks of the trial, the percentage of patients taking antacids was higher in the placebo-treated than in the famotidine-treated patients (figure 36). The mean number of days of antacid therapy (table 16) and the mean number of antacid tablets taken daily (table 17) were statistically significantly fewer at most intervals with famotidine than with placebo, but the differences were not clinically significant. For example, patients on placebo took less than one antacid tablet per day fewer throughout the 8 weeks of treatment than did the patients receiving famotidine 40 mg h.s., the dose recommended for the short-term treatment of duodenal ulcer. The mean number of days in which patients took antacids was less than one day more over an 8 week period with placebo than with the 40 mg h.s. dose.

Figure 36
Percentage of Patients Receiving Antacid Therapy

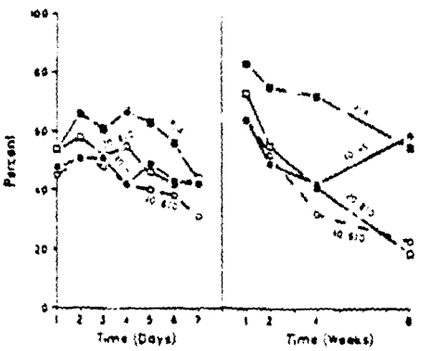


TABLE 16

Mean Days of Antacid Therapy, Mean ± Standard Deviation

WEEK	FAMOTIDINE 40 HS N	FAMOTIDINE 40 HS MEAN	FAMOTIDINE 20 BID N	FAMOTIDINE 20 BID MEAN	FAMOTIDINE 40 BID N	FAMOTIDINE 40 BID MEAN	PLACEBO N	PLACEBO MEAN	NUMBER OF DAYS DIFFERENCE BETWEEN 40 HS & PLACEBO
1	92	3.3 ± 3.06	84	3.5 ± 2.80	93	2.9 ± 2.86**	98	4.1 ± 2.64	-0.8
2	87	2.7 ± 3.05**	80	2.5 ± 2.81**	84	2.0 ± 2.53**	95	3.6 ± 2.79	-0.9
4	56	2.2 ± 2.82**	45	1.9 ± 2.69**	51	1.3 ± 2.28**	70	3.1 ± 2.67	-1.1
8	21	2.9 ± 2.98	18	1.0 ± 2.22**	12	0.8 ± 1.42**	37	2.8 ± 2.89	+0.1

** Significantly different from placebo, p ≤.01.
+ Significantly different from 20 BID, p ≤.05 and significantly different from 40 BID, p ≤.05.

TABLE 17

Number of Antacid Tablets Taken Daily, Mean ± Standard Deviation

Week	Famotidine 40 HS N	Famotidine 40 HS Mean	Famotidine 20 BID N	Famotidine 20 BID Mean	Famotidine 40 BID N	Famotidine 40 BID Mean	Placebo N	Placebo Mean	Difference Between 40 HS & Placebo
1	92	1.7±2.15**	84	1.5±2.35	93	1.6±2.15**	98	2.2±2.05	-0.5
2	87	1.4±1.99**	80	1.4±1.90**	84	0.9±1.61**	95	2.1±2.34	-0.9
4	56	1.0±1.71**	45	1.0±1.97**	51	0.6±1.23**	70	1.7±1.94	-0.7
8	21	1.2±1.41	18	0.7±2.13**	12	0.3±0.71*	37	1.4±1.79	-0.2

*,** Significantly different from placebo, p≤.05, p≤.01, respectively.

(g) Summary: this trial of the short-term (up to 8 weeks) healing of duodenal ulcer compared famotidine in doses of 40 mg h.s., 20 mg b.i.d. and 40 mg b.i.d. with placebo in a total of 384 patients of whom 366 were evaluable for effectiveness. Healing, defined as complete re-epithelization of the ulcer site regardless of the persistence or emergence of duodenitis and/or erosions, was evaluated at 2, 4 and 8 weeks, depending on the interval at which the ulcer was found to be healed.

The incidence of healing was highly significantly better than placebo with all doses at all treatment weeks (p 0.001). With the doses of 40 mg h.s., 20 mg b.i.d, 40 mg b.i.d. and placebo, the crude incidence of healing of ulcer was 83%, 82%, 82% and 45% respectively. The respective percentages as calculated by life-table analysis were 88%, 89%, 89% and 55%.

The drug groups showed significant reduction in day and night pain compared to placebo (p 0.001) and in the consumption of antacids. However, the differences between famotidine and placebo in the amount of antacid consume and the number of days antacid were taken was not clinically significant.

The most common clinical adverse experiences were headache (5.2%) and constipation (3.1%) in the group receiving 40 mg h.s. as contrasted with respective incidences of 11.0% and 1.0% in the placebo group. Eight of 284 patients (3%) receiving famotidine and 5 of the 100 receiving placebo (5%) were withdrawn because of clinical adverse experiences.

Serious clinical adverse experiences reported during the study were either complications of pre-existing conditions or were the result of treatment failure. Serious laboratory adverse experiences were no more frequent in the famotidine groups than in the placebo group.

Based on the results of this study the sponsor recommends a 40 mg h.s. dosage regimen for the short-term therapy of duodenal ulcer.

2. Protocol number: none assigned

a. Title of study: famotidine in the prevention of recurrence of duodenal ulcer.

b. Design of study: double-blind, randomized, multi-center, placebo-controlled dose-ranging study. Patients who had a healed ulcer in the short-term treatment period were invited to enter this (maintenance) phase of the study. The patients were re-randomized to treatment with either famotidine 40 or 20 mg h.s. or placebo. Patients were re-endoscoped after 4 weeks (up to 42 days on treatment), 12 weeks (days 43-105) and 24 weeks (day 106 and later), unless symptomatic relapse called for endoscopic examination before the scheduled return visit.

c. Investigators: twenty-four of the 34 investigators who participated in the short-term trial participated in this trial. Fifteen of the investigators contributed 5 or fewer patients, while only 7 contributed 10 or more. The success of the investigators in enrolling eligible patients into the long-term trial varied over a considerable range from 55 to 88%.

d. Results

(1) Comparability of the patient groups: 54 patients were allocated to 40 mg h.s., 57 to 20 mg h.s. and 66 to placebo. The treatment groups were comparable in all essential respects (table 18).

TABLE 18

Comparability of Treatment Groups

	FAMOTIDINE 40 HS (N=54)	FAMOTIDINE 20 HS (N=57)	PLACEBO (N=66)
Age (Years), Mean	50.6**	46.6	43.3
Sex			
Females	14 (26%)	15 (26%)	17 (26%)
Males	40 (74%)	42 (74%)	49 (74%)
Treatment in Acute Study			
Famotidine 40 HS	14 (26%)	18 (32%)	17 (26%
Famotidine 20 BID	16 (30%)	15 (26%)	12 (18%
Famotidine 40 BID	15 (28%)	16 (28%)	22 (33%
Placebo	9 (17%)	7 (12%)	15 (23%)
Week Ulcer Healed in Acute Study			
Week 2	29 (54%)[a]	26 (46%)	25 (38%)
Week 4	20 (37%)	20 (35%)	31 (47%)
Week 8 or Later	5 (9%)	11 (19%)	10 (15%)
Smoking	31 (57%)	40 (70%)	42 (64%)
Drinking	12 (22%)	8 (14%)	14 (21%)
Initial Ulcer Size, Mean	0.82	0.89	0.90
Number of Ulcers			
One	42 (78%)	49 (86%)	60 (91%)
Two or More	12 (22%)	8 (14%)	6 (9%)
Age at First Ulcer (Years), Mean	43.5*,+	37.7	36.1
Duration of Ulcer Disease (Years), Mean	7.0	8.8	7.3
Ulcer History			
None	25 (46%)	21 (37%)	21 (32%
One Previous Episode	17 (31%)	22 (39%)	24 (36%
Multiple Previous Episodes	12 (22%)	14 (25%)	21 (32%
Other Pathology in Esophagus	13 (25%)	13 (23%)	19 (29%
Other Pathology in Stomach	13 (25%)[b]	7 (12%)	9 (14%
Other Pathology in Duodenum	30 (57%)	30 (53%)	30 (45%

*,** Significantly different from placebo group, $p<0.05$, $p<0.01$ respectively.
+ Significantly different from famotidine 20 HS group, $p<0.05$.
a,b Different from Placebo group, $p=0.08$, $p=0.10$ respectively.

(2) Exclusions from analysis for effectiveness (table 19): the most frequent reason for exclusion was failure to take the prescribed medication for various periods of time at various intervals of the trial. The proportion of patients excluded from the analysis for effectiveness of 40 mg h.s., 20 mg h.s. and placebo was respectively 9%, 14% and 6% which is not a bad record for a 6 month trial. In addition to these exclusions a number of patients dropped out at at various intervals during the trial for various reasons; the sponsor's accounting for these patients is a matter to be addressed by our biometricians.

TABLE 19

Exclusions from Analysis of Effectiveness

	Treatment 40 HS N = 54	20 HS N = 57	PLA N = 66
Off drug[a]	3	4	4
Off drug[b]	1	2	0
Off drug[c]	0	1	0
Protocol deviation	1	1	0
Total	5 (9%)	8 (14%)	4 (6%)
Included in analysis for effectiveness	49	49	62

a More than 7 consecutive days
b More than 5 days during weeks 1-4
c More than 10 days during weeks 5-12

(3) Safety

(a) Vital signs (table 20): the only statistically significant change from baseline was an increase in mean systolic BP from 121.7 to 126.1 in patients receiving 20 mg h.s. It is doubtful whether this has any clinical importance.

TABLE 20

Effect of Treatment on Vital Signs, Mean values

Measurement	Treatment Group	N	Baseline	Endpoint	Change from baseline
Body weight (lbs)	Famotidine 40 HS	45	174.2	172.3	-1.9
	Famotidine 20 HS	47	169.6	171.5	1.9
	Placebo	34	168.0	168.2	0.2
Pulse (beats/min)	Famotidine 40 HS	54	73.1	72.0	-1.2
	Famotidine 20 HS	52	74.6	73.5	-1.1
	Placebo	64	72.9	75.8	2.9
Systolic Blood Pressure (mmHg)	Famotidine 40 HS	54	121.6	122.2	0.6
	Famotidine 20 HS	52	121.7	126.1	4.4*,+
	Placebo	65	123.3	120.9	-2.4
Diastolic Blood Pressure (mmHg)	Famotidine 40 HS	54	76.5	76.1	-0.4
	Famotidine 20 HS	52	79.1	79.4	0.3
	Placebo	65	76.3	77.6	1.3

* Significantly different from placebo group, $p < .05$
\+ Significant change from baseline, $p < .05$
B Change from baseline, $0.05 \leq p \leq 0.10$.

(b) Clinical adverse experiences: the incidence of adverse signs/symptoms was similar in the 3 groups (40 h.s. 23%, placebo 29%). The number withdrawn because of adverse experiences was no greater with famotidine (4/111, 4%) than with placebo (6/66, 10%).

Adverse clinical experiences classified by body system (table 21) or by symptoms (table 22) were generally no more frequent in patients receiving famotidine than in those receiving placebo.

TABLE 21

Clinical Adverse Experiences

Body System	Famotidine 20 MG (N = 57)	Famotidine 40 MG (N = 54)	Placebo (N=66)
Body as a whole	0	2 (3.7%)	1 (1.5%)
Central nervous	5 (8.8%)	6 (11.1%)	7 (10.6%)
Cardiovascular	0	1 (1.9%)	0
Digestive	6 (10.5%)	7 (13.0%)	11 (16.7%)
Respiratory	3 (5.3%)	3 (5.6%)	5 (7.6%)
Tegumentary	2 (3.5%)	1 (1.9%)	3 (4.5%)
Musculoskeletal	4 (7.0%)	2 (3.7%)	1 (1.5%)
Special Senses	1 (1.8%)	1 (1.9%)	1 (1.5%)
Urogenital	1 (1.8%)	2	0

TABLE 22

Clinical Adverse Experiences with 2% Incidence

	Famotidine 20 MG N = 57	Famotidine 40 MG N = 54	Placebo N = 66
Abdominal Pain	3 (5.3%)	3 (5.6%)	4 (6.1%)
Headache	2 (3.5%)	4 (7.4%)	4 (6.1%)
Constipation	2 (3.5%)	1 (1.9%)	2 (3.0%)
Back Pain	2 (3.5%)	1 (1.9%)	0
Pruritis	2 (3.5%)	0	0
Constipation	1 (1.8%)	2 (3.7%)	1 (1.5%)
Paresthesia	1 (1.8%)	2 (3.7%)	0

(c) Serious clinical adverse experience were reported in 3 patients:

A 59 year old male with hypertension and atherosclerosis receiving famotidine 40 mg h.s. was admitted to the hospital on day 69 with a 2-week history of a severe right-sided head and face pain with 3 to 4 episodes of transient blindness in the right eye. A CT scan demonstrated a recent infarct in the distribution of the right middle cerebral artery. Angiography showed complete occlusion of the right, and partial occlusion of the left internal carotid. Therapy with famotidine was discontinued. The investigator considered this experience not drug-related.

A 50 year old male with a prior history of hemoptysis was receiving famotidine 40 mg h.s. when a diagnosis of pulmonary tuberculosis was made and the drug was discontinued on study day 36. The investigator believed the experience was definitely not related to drug therapy.

A 61 year old female with chronic obstructive pulmonary disease was admitted to the hospital with non-specific chest pains of 2 days duration after 42 days on placebo. The patient has been lost to follow-up. The investigator considered the experience definitely not drug-related.

(d) Laboratory adverse events were not serious and were no more frequent in the famotidine-treated patients than in the placebo-treated patients (table 23). There were 2 withdrawals from the trial in the famotidine group, one in the placebo group because of adverse laboratory events, but a drug-relationship was extremely doubtful in all cases.

TABLE 23

Laboratory Adverse Events/Number at Risk

	Famotidine 20 MG N=57	Famotidine 40 MG N=54	Placebo N=66
Hematology	3/52	5/54	1/64
Renal Function	0/51	3/53	0/64
Liver Function	11/51	3/53	13/64
Metabolic	3/51	0/54	0/60
Urogenital	3/51	6/54	9/60

(4) Effectiveness

(a) Incidence of recurrence: the sponsor's tabulation divides the duration of treatment into 3 periods, days 1-42, 43-105 and 106 or later (table 24). By life-table analysis it is clear that the incidence of recurrence with placebo (67%) is statistically significantly higher at the end of the 6 month trial than that with famotidine 40 mg h.s. (31%) and 20 mg h.s. (26%). However, because of the wide spread of the intervals allowed for the respective periods (e.g., period 3, the 6-month interval, includes endoscopies performed from day 106 onward) an endoscopic finding at 15 or 16 weeks would be included in the 24 week analysis. To get some conception of the rate as well as the incidence of recurrence, I requested the sponsor to prepare a tabulation showing the numbers for each 4-week period (table 25). From these data it is clear that, as has been shown in

TABLE 24

Cumulative Percent Recurrence: Life-table Analysis

	40 HS	20 HS	PLACEBO
Period 1 (days 1-42)	0	1.8	12.1
Period 2 (days 43-105)	15.2	17.8	51.4
Period 3 (days 106 or later)	30.6	25.5	66.7

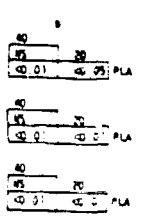


TABLE 25

Number of Patients who Relapsed (%)* (Life Table Rate)

	FAMOTIDINE 40 HS (N=54)	FAMOTIDINE 20 HS (N=57)	PLACEBO (N=66)
Month 1 (Days 1-28)	0 (0)	0 (0)	1 (.5)
Month 2 (Days 29-56)	1 (2)	1 (2)	10 (16)
Month 3 (Days 57-84)	2 (4)	1 (2)	13 (22)
Month 4 (Days 85-112)	5 (10)	5 (10)	30 (54)
Month 5 (Days 113-140)	8 (19)	10 (21)	33 (62)
Month 6 (Days 141-168)	8 (19)	10 (21)	34 (64)
After month 6 (Days 169-231)	11 (22)	12 (26)	35 (67)

*All Patients Treated Analysis

previous trials of prevention of recurrence, the recurrences tend to occur within the first 4 months. The bottom line, however, remains the same, in that the data provide evidence of effectiveness of famotidine in both dosages in reducing the incidence of recurrence of duodenal ulcer.

(b) Antacid consumption: the percent of patients taking antacids during the trial was the same on famotidine 40 h.s. (12%), 20 h.s. (14%) and placebo (15%).

e. Summary: 177 of the patients whose duodenal ulcers had healed in the short-term trial were admitted to a one year trial of famotidine, 40 mg h.s., 20 mg h.s. or placebo in the prevention of recurrence. At the time of this submission data were insufficient to report on the results beyond 6 months. The limited achievement of short-term healing is illustrated by the 67% incidence of recurrence in 6 months in patients receiving placebo. Both doses of famotidine reduced the incidence by about the same order of magnitude; the sponsor's recommended "maintenance" dose, 20 mg h.s., yielded a 26% incidence of recurrence. In this trial the drug was safe; clinical and laboratory adverse experiences were no more frequent in patients receiving the drug than in those receiving placebo.

f. Comment: bringing about healing of the duodenal ulcer in the short-term is no great clinical problem; it can be achieved as well with a few daily doses of antacid as with any of the systemically acting drugs. The problem in peptic ulcer disease is to prevent recurrence and thereby avoid intractability. Famotidine is clearly superior to placebo in this respect

but the 21% incidence of recurrence within 6 months with the recommended dose of 20 mg h.s. still leaves quite a bit to be desired. To compare the effectiveness of famotidine with that reported for other drugs it will be necessary to await the completion of the 1-year trial.

A single bedtime dose would have a cost-effective advantage, but as for the contention that it improves compliance, I doubt that patients would be any less compliant with a regimen of one tablet in the morning and one tablet in the evening. Since it may be possible to achieve even greater effectiveness in the prevention of recurrence than was obtained in this trial, the sponsor should consider a trial of a dose of 40 mg b.i.d., or perhaps 40 mg in the morning and 20 mg in the evening.

3. Study No. 41

a. Title: An open-label study to evaluate the use of famotidine in patients with peptic ulcer, Zollinger-Ellison Syndrome resistant to or intolerant of cimetidine or ranitidine or both.

b. Design of study: Open-label, uncontrolled study.

c. Investigator: Sidney Cohen, M.D., Hospital of the University of Pennsylvania, Philadelphia, PA.

d. Results (table 26)

(1) Characteristics of patients entered into the study: the basal acid output in the first 3 patients in the table is surprisingly low, especially in the face of the elevated serum gastrins.

(2) Safety: two of the patients had adverse effects, both requiring discontinuation from the study. One patient had severe abdominal pain, the other elevated liver enzymes which, however, were not clearly attributable to famotidine since the patient had had multiple blood transfusions and the enzymes were slightly elevated prior to entry into the study.

(3) Effectiveness: famotidine controlled the symptoms in all patients on doses titrated to the individual patient; doses as high as 400 mg/day were required. Three patients had been receiving famotidine for approximately one year at the time of this report (January 25, 1984).

e. Summary: a satisfactory response to therapy was achieved in 7 patients with possible or proven Z-E syndrome who had not been adequately controlled or had had adverse effects on cimetidine or ranitidine.

f. Conclusions: famotidine was usually well tolerated in patients with Z-E syndrome and may be useful in patients resistant to or intolerant of other H_2-blockers.

TABLE 26

Zollinger-Ellison Patients Treated With Famotidine

Patient	Age	Sex	BAO mEq/hr	MAO** mEq/hr	Gastrin pg/ml	Diagnosis	Concomitant Conditions	Previous Therapy	Reason Previous Therapy Discont.	Final Dose mg	Duration of Therapy	Adverse Events
1	64	M	1.8	19.3	700	Probable Z-E	Sick sinus syndrome, asthma	Cimetidine	Serum Creatinine Gynecomastia	60 BID	yr	
2	44	M	10.2+		481	Z-E	MEA, hyperthyroidism	Cimetidine Ranitidine	Recurrent ulcer on medication	160 AM 40 PM	1 yr	
3	63	F	7.5		500	Z-E	None	Cimetidine Ranitidine	Decreased effectiveness on cimetidine Recurrent ulceration on ranitidine	20 BID	1 yr	
4	43	M	75	90	1762	Z-E	Hypertension	Cimetidine Ranitidine	Severe abdominal pain	N/A	1 day	Severe abdominal pain discontinued from study
5	26	M	37.3	65.3	791	Z-E	None	Cimetidine Ranitidine	Recurrent pain and ulcer on cimetidine	80 BID	4 wks	
6	47	M	4.5 (Tumor Metastasis)			Z-E	None	Cimetidine Ranitidine	CNS side effect Recurrent acute gastric ulcers on cimetidine	20 QID	2 mo	Liver enzymes elevated, discontinued from study
7	53	F	61.0		676	Z-E	COPD anxiety hives	Cimetidine Ranitidine	Decreased effectiveness on cimetidine	40 BID	1 mo	

*BAO-Basal acid output per hour, **MAO-Maximal acid out per hour -Obtained in 1981

4. Study No. 6

a. Title of study: the use of famotidine in patients with hypersecretion of acid.

b. Investigator: Robert T. Jensen, M.D., Digestive Disease Branch, NIH, Bethesda, MD.

c. Design of study: open study divided into an acute phase and a long-term phase. The acute phase was conducted to compare the potency, onset of action, and duration of action of famotidine with cimetidine and ranitidine. A non-randomized block design was used.

Patients included in the study met the criteria of Zollinger-Ellison syndrome defined by a basal gastric acid output greater than 15 mEq/hr, a fasting serum gastrin concentration of greater than 100 pg/ml (normal less than 100 pg/ml), and a rise in the serum gastrin concentration of greater than 200 pg/ml after intravenous infusion of 2 units/kg of secretin. Patients under 18 years of age or women capable of becoming pregnant were excluded.

The critical evaluation criterion in this study was the level of hourly gastric acid output. An effective dose was defined as that which maintained the gastric acid secretion below 10 mEq/hour in the sixth hour following a dose.

At the start of the study, H_2-blockers were discontinued and gastric acid secretion was followed until it rose above 10mEq/hour. At that time, famotidine 20 to 60 mg was given every six hours for at least 4 doses. Selection of the starting dose of famotidine was based on the patient's response to previous treatment with H_2-blockers. Famotidine dosage was adjusted by 20 mg increments every 6 hours until the gastric acid output during the sixth hour post-drug was below 10 mEq. This dose was continued through the next day and gastric secretion measured again to ensure suppression of gastric acid to below 10mEq/hour.

In summary, based on the animal findings, Famotidine is predicted to be a very potent, very selective, long-acting and competitive H_2 receptor antagonist. The data also predict an unusually safe compound with a therapeutic index superior to cimetidine or ranitidine. It will likely compare to ranitidine and contrast with cimetidine in being devoid of anti-androgenicity and significant drug interaction complications. It should be like cimetidine and ranitidine and unlike metiamide in lacking a significant potential for agranulocytosis. Freedom from cardiovascular complications with oral use may be a unique advantage for F. Despite its extraordinary potency and somewhat longer duration of action, Famotidine does not seem to have any potential to cause sustained gastric achlorhydria, sustained hypergastrinemia, gastric ECL hyperplasia, or gastric carcinoids when administered once a day regardless of dose. In oral carcinogenicity studies of approximately 2 years duration in mice and rats up to 2000 mg/kg, (2000 times HD), it demonstrated no carcinogenic potential in any organ, the stomach, liver, and testes included.

In conclusion, Famotidine has been thoroughly investigated in animals and has clearly demonstrated efficacy and reasonable safety. Accordingly, this well-organized and very readable NDA (#19-462)by Merck Sharpe and Dohme for Pepcid(famotidine) Tablets is approvable from the preclinical standpoint.

The only recommendations offered are that the labeling:

1. warn against use by nursing mothers since in rats Famotidine accumulates in the milk, penetrates the blood-brain barrier of neonates with relative ease, and causes extended growth depression in nursing offspring.

2. suggest lowering of dose in patients with impaired kidney function since in rats, dogs and humans, absorbed drug is eliminated almost exclusively in the urine.

Pierre Deslauriers

Pierre Deslauriers, Pharmacologist

cc: Orig. NDA 19-462
HFN-110
HFN-110/CSO
HFN-110/PDeslauriers
HFN-102/VCGlocklin
HFN-345/GWCumes
f/d init. PJDeslauriers,Act.Superv.Pharm.
cb:kg:rq:0705v:1-8-86

HFN-110 Dr Barbour
HFN-110 Dr Stern

9.

NOV 1 1984

[redacted]

September 13, 1984

Review and Evaluation of Animal Data
(Amendments of April 6, 1984)

The amendment supplies the following additional animal date:

1. Three month range-finding study in mice: Groups of 15 M and 15 F mice were gavaged once daily with MK-208 at levels of 0, 100-200, 400 700-1500, and 1000 mg/kg for 3 months in a study intended to find suitable doses for a carcinogenicity study.

   Results:

   Due to lack of toxicity, some dose levels were increased at five weeks. Viscosity limited the maximum dose to 2000 mg/kg. The drug was apparently very well tolerated at all levels, survival and growth being undisturbed. Necropsies were not done.

2. Ninety two week carcinogenicity study in mice: Groups of 50 M and 50 F Charles River mice were given MK-208 in suspension by gavage once daily at levels of 20, 200, and 2000 mg/kg/day (2000 times the daily human dose) for 92 weeks.

   Results:

   All treated groups performed as well as controls, the treated were like controls with respect to survival, growth, ophthalmoscopic exams, and gross and histologic findings except that diffuse distention of the glands of the fundus of the stomach was noted in 42% of the females at the top dose vs 11% among controls. There was no specific tumor that was statistically more prevalent in the test groups vs controls. There was no indication of carcinogenicity in either the stomach or testes. The only suspect finding was the occurrence of adenoma or adenocarcinoma of the lung in 31 of 100 low dose animals vs. 22/100 and 15/100 in the two control groups; however, the incidence at the mid and high dose was like the controls.

3. One hundred and six week carcinogenicity study in rats: Groups of 50 M and 50 F rats were gavaged with 20, 200, and 2000 mg/kg of MK-208 in suspension for 106 weeks. Two control groups each of similar number were used.

Results:

Again the test groups performed like controls. Morbidity among the males was slightly higher than controls at each test level and among the females as well at the top dose. For example, the percent of rats that died or were sacrificed before termination was 64%, 76%, 78% and 76% among the C,L,M, and H dose males and 42%, 48%, 52% and 72% among the respective females. Some of these deaths in the test groups were most likely due to accidental lung intubation considering the higher incidence of foreign body material in the lungs of animals at the upper two levels. Growth was unaffected and ophthalmoscopic exams were normal. Gross and histologic exams did not show carcinogenicity in any organ, the stomach and testes included. The only questionable finding was endometrial polyp in 3/50, 1/50, and 1/50 females at the high, mid, and low doses vs 0/100 control females, this tumor however was not statistically significant. Non-neoplastic changes that were drug related included: glandular tissue distertion in 5/50, 3/50, and 10/50 females from the low, mid and high dose levels vs 1/100 control females, nuclear enlargement of glandular mucosa in 9/100 and 26/100 from the mid and high doses vs 7/200 controls, eosinophilic cytoplasmic granularity of zymogen chief cells in 23/100 and 49/100 from the mid and high doses vs 25/200 controls. The sponsor considers all of the foregoing changes as "physiologic alterations related to the pharmacologic activity of the test article, i.e. inhibition of pepsin turnover secondary to inhibition of acid secretion".

EVALUATION:

The ninety two week carcinogenicity study in mice and the 106 week carcinogenicity study in rats did not show MK-208 to be carcinogenic in either species tested approximately two yrs. with daily dosages ranging to 2000 mg/kg or 2000 times the human dose of 1mg/kg/day. It was notable that there was no evidence of carcinogenicity in either the stomach or testes.

Because some H2 receptor antagonists have produced stomach and testicular tumors near the end of a rodent's lifetime, it would have been preferable if these studies were lifespan studies. Since however they gave not even a suggestion of tumors in either organ after a fairly lengthy period of time (which extended over most of the animals' lifespan), the submitted studies appear to reasonably exclude the possibility of carcinogenicity.

Pierre Deslauriers

Pierre Deslauriers, Ph.D.

cc:Orig
HFN/110
HFN/110/CSO
HFN/110/PDeslauriers
cb/10/22/84/3628c
R/D: C.A.Resnick
Dr Bachrach
Dr. Stern

CHEM REV

DIVISION OF CARDIO-RENAL DRUG PRODUCT
CHEMIST'S REVIEW #3

Date Completed: March 31, 1986

A. 1. NDA 19-462:

Sponsor: Merck Sharp and Dohme

Address: West Point, Penn 19486

AF #: 12-611

2. Product Name (s):

Proprietary- Pepcid

Nonproprietary- Famotidine

USAN- as above

Compendium- none listed

Code Name and/or number-
Refer to Chemist's Review [redacted]

3. Dosage Form and Route of Administration:
Oral tablets of 20 and 40 mg deveoped for marketing.

4. Pharmacological Category and/or Prinicpal Indications:

Potent, long-acting H_2 receptor antagonist (healer to peptic ulcers).

5. Structural Formula and Chemical Name:
See Chemist Review #1

B. 1. Initinal Submission: Receipt Date: 06-24-85
Filing Date: 08-22-85

c. Remarks:

b. Conclusions.

This application is now considered to be approvable from the standpoint of manufacturing controls. The SBA has been changed to reflect this under the "Methods Validation" section.

Stuart Zimmerman

Stuart Zimmerman, Ph.D.

4-1-86

cc:
ORIG
HFN-110
HFN-110/CSO
HFN-110/SZimmerman/4/3/86
cb/4/3/86/0871v
R/D init RWolters/4/8/86

The minimum 6-hourly doses of cimetidine and ranitidine were determined similarly; the adjustment increment of cimetidine was 300 mg, of ranitidine 150 mg, every 6 hours.

If doses of more than 160 mg of famotidine, 1600 mg of ranitidine, or 3,600 mg of cimetidine were required every 6 hours, the patient was defined as resistant to the respective drug and an anticholinergic, isopropamide 5 mg, was given every 6 hours in addition to the H_2-blocker. The minimum 6-hourly dose requirements were then determined as described above. The minimum doses of each drug that reduced gastric acid secretion to the same degree (to below 10 mEq/hr during the sixth hour after a dose) were considered equipotent.

In the long-term phase patients were treated continuously with famotidine alone for up to 38 weeks to investigate the safety, tolerability and required adjustments of the famotidine maintenance dose. They were evaluated at two weeks, two months and thereafter at [illegible]o monthly intervals after beginning famotidine therapy. The initial dose was the minimum dose identified in the short-term study. Dosage was titrated as needed to ensure continued suppression of gastric acid below 10 mEq/hour.

d. Results

(1) Characteristics of patients studied (table 27): 11 patients were evaluated. It is obvious that they were all sick people.

TABLE 27

Characteristics of Patients Treated with Famotidine

Pt No	Age	Sex	Disease Duration (Yrs.)	Tumor Status	Prior Antisecretory Therapy	Basal Acid Output (mEq/Hr)	Gastrin Basal (pg/ml)	Secondary Diagnoses
1	48	M	1	None	Ranitidine 300 BID	55.6	184	Peripheral vascular disease, chest pain
2	61	M	1	Suspected	Cimetidine	60.1	4,100	Liver cyst, obesity, diabetes, low back pain
3	55	M	1	None	Ranitidine	28.4	87.44	Myocardial infarction, borderline diabetes, chronic bronchitis
4	54	M	1	Proven*	Ranitidine	44.6	14,10,000	Diabetes, Gilbert's Syndrome
5	65	M	6	Suspected	Ranitidine	35.0	1,180	Cancer of prostate, hypertension
6	22	M	2	Proven*	Ranitidine	44.4	5,20,540	Deep vein thrombosis
7	66	F	5	None	Cimetidine 300 BID	14.5	630	Obesity, hypertension
8	54	M	5	None	Cimetidine 300 BID	28.1	345	Multiple sclerosis, Barrett's esophagus, ulcer 30 yrs. ago, alcohol liver disease
9	47	F	2	Proven*	Cimetidine	8.1	300	Obesity, hypertension, DM, psoriasis, cystic [illegible]
10	55	M	1	Suspected	Ranitidine 300 BID	50.0	2,700	Hypertension, asthma, mild prostatic hypertrophy
11	66	M	1	None*	Ranitidine	38.2	615	Mild chronic renal failure, alcoholic, severe fatty liver
Mean						44.2	4,041	Lower motor neuron disorder

*Laparotomy performed. Hypersplenic tail resection resected

(b) Laboratory adverse events: famotidine was discontinued in 2 patients, one after 160 days with increased SGPT which was present at the outset and one after 241 days with marginal eosinophilia, elevated ESR and leukopenia.

(2) Effectiveness

(a) Relative potency of famotidine vs cimetidine and ranitidine: famotidine averaged 34 times as potent as cimetidine (range 15-75), 9 times as potent as ranitidine (range 2.5-15).

(b) Onset of action (figure 37): there was no difference among the 3 drugs in the rate of onset of action.

(c) Duration of action (figure 38): mean hourly gastric acid output remained below 10 mEq for 8 hours post-famotidine administration while the mean acid output at that interval was about 12 mEq with both cimetidine and ranitidine, not an impressive difference. From the 10th to 12th hours, however, acid was more effectively suppressed with famotidine than with either of the other drugs.

Figure 38
Duration of Action of Famotidine, Cimetidine, and Ranitidine

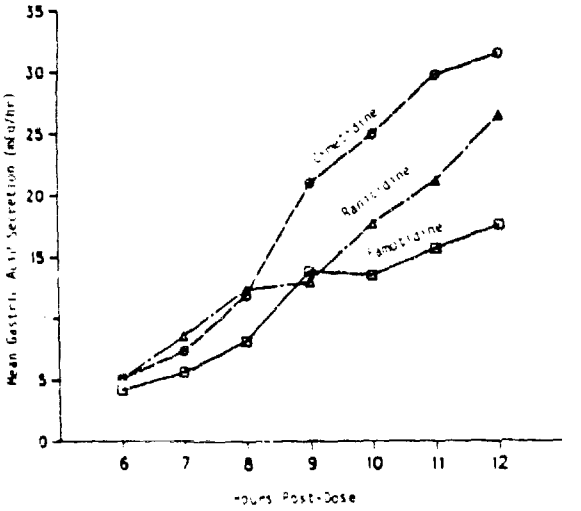
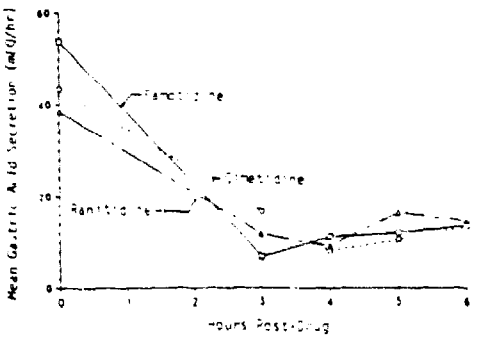


Figure 37
Onset of Action of Famotidine Compared with Cimetidine and Ranitidine (N = 4)



e. Summary: The summary and conclusions are set forth succinctly in the published paper by Howard et al (Gastroenterology 1985; 88:1026-1033, reprint attached). Famotidine was similar to the two other H_2-blockers in that equipotent doses had the same onset of action, time to maximum activity, patient tolerance, lack of evidence of hepatotoxicity and hematotoxicity, requirement for periodic adjustment of dose, and correlation among individual daily doses required to control gastric secretion. Famotidine differed from the other two drugs in that it had a longer duration of action, possibly attributable to a longer occupation of the H_2-receptor site,which, however, does not necessarily result in a less frequent dosing interval. Famotidine differed from cimetidine in that long-term high-dose treatment in males was not associated with anti-androgen side effects.

B. Foreign clinical trials

1. Study No. 5006

a. Title of study: 'A double-blind study in out patients to compare famotidine with ranitidine in the short-term treatment of duodenal ulceration.

b. Design of study: the protocol for this trial was identical to that outlined for the U.S. multicenter trial except that (1) instead of placebo, the reference control treatment was ranitidine 150 mg b.i.d, and (2) scores for severity of pain and of other symptoms were defined:

(1) Day pain

0 none
1 mild = bothered a little; pain is present part of the day, but causes little or no discomfort.
2 moderate = bothered to some degree; pain is present most of the day, annoying, but not interfering with daily routine.
3 severe = bothered intensely; constant pain causing marked interference with daily routine.

(2) Night pain

0 none
1 mild = bothered a little; pain is present part of the night, but does not interfere with sleep.
2 moderate = bothered to some degree; pain is present most of the night, occasionally interferes with sleep.
3 severe = bothered intensely; constant pain, marked interference with sleep.

(3) Other symptoms

(a) abdominal discomfort
(b) feeling of fullness
(c) flatulence
(d) acid regurgitation
(e) heartburn
(f) nausea
(g) vomiting
(h) other

(4) Severity of these symptoms was scored as follows:

0 none
1 mild = awareness of sign or symptom, but easily tolerated.
2 moderate = discomfort enough to cause interference with usual activity.
3 severe = incapacitating with inability to work or carry out usual activity.

(5) Global response to therapy was assessed by the patient as follows:

4 excellent = best possible anticipated response; abdominal pain completely relieved, other symptoms improved or no worse than usual.

3 good = good response; abdominal pain almost completely relieved, other symptoms improved or no worse than usual.

2 fair = definite response, but could be better; some relief of abdominal pain, other symptoms unchanged or worse.

1 poor = minimal response; little or no relief of abdominal pain, other symptoms unchanged or worse.

0 none = no response, absence of drug affect.

(5) The dosage schedule was as follows (all doses in milligrams):

Treatment Group	8:00 AM	10:00 PM
Famotidine 40 h.s.	placebo famotidine placebo ranitidine	famotidine 40 placebo ranitidine
Famotidine 20 b.i.d.	famotidine 20 placebo ranitidine	famotidine 20 placebo ranitidine
Famotidine 40 b.i.d.	famotidine 40 placebo ranitidine	famotidine 40 placebo ranitidine
Ranitidine 150 b.i.d.	placebo famotidine ranitidine 150	placebo famotidine ranitidine 150

c. Investigators (table 28): 68 investigators in 19 countries, all qualified by training and experience to conduct clinical trials, participated in this study.

d. Results

(1) Comparability of treatment groups (table 29): the number of patients in the respective groups were famotidine 40 h.s. 255, 20 b.i.d. 259, 40 b.i.d. 258, ranitidine 150 b.i.d. 259. The four treatment groups were essentially comparable in numbrs and in all other respects. There was no significant difference in the mean age between males and females.

TABLE 29

Comparability of Treatment Groups

	FAMOTIDINE 40 HS (N=255)	FAMOTIDINE 20 BID (N=259)	FAMOTIDINE 40 BID (N=258)	RANITIDINE 150 BID (N=259)
Age (Years) Mean	43.5	43.1	42.1	45.4
Sex				
Male	177 (69%)	177 (67%)	195 (76%)*	195 (75%)*
Female	78 (31%)	86 (33%)	63 (24%)	64 (25%)
Weight (kg) Mean	64.5	66.6	65.8	64.3
Smoking	155 (61%)	150 (58%)	160 (62%)	148 (57%)
Alcohol	128 (50%)	121 (47%)	114 (44%)	121 (47%)
Initial Ulcer Size (cm²) Mean	0.96	0.91	0.94	0.91
Number of Ulcers				
One	225 (88%)	230 (89%)	233 (90%)	232 (90%)
Two or More	30 (12%)	29 (11%)	25 (10%)	26 (10%)
Age at First Ulcer (Years) Mean	38.4	38.0	37.7	38.9
Duration of Ulcer Disease (Years) Mean	5.5	5.0	5.4	6.0
Ulcer History				
None	75 (29%)	77 (30%)	79 (31%)	71 (27%)
One Previous Episode	75 (29%)	65 (25%)	67 (26%)	62 (24%)
Multiple Previous Episode	105 (41%)	117 (45%)	112 (43%)	126 (49%)
Other Pathology in Esophagus	25 (10%)	32 (12%)	32 (12%)	31 (12%)
Other Pathology in Stomach	51 (20%)	50 (19%)	54 (21%)	64 (25%)
Other Pathology in Duodenum	113 (44%)	108 (42%)	121 (47%)	113 (44%)
Concomitant Conditions				
Anemia	6 (2.4%)	3 (1.2%)	0	0
Anxiety Disorders	2 (0.8%)	4 (1.5%)	4 (1.6%)	8 (3.1%)
Asthma	1 (0.4%)	3 (1.2%)	6 (2.3%)	4 (1.5%)
Cholecystectomy	5 (2.0%)	10 (3.9%)	7 (2.7%)	4 (1.5%)
Hypertension	13 (5.1%)	16 (6.2%)	10 (3.9%)	14 (5.4%)
Insomnia	5 (2.0%)	3 (1.2%)	0	1 (0.4%)

*Significantly different from the famotidine 20 BID group ($p<0.05$)

Four patients with more than one ulcer. This was the size of the largest ulcer.

One patient did not have a duodenal ulcer.

N=254, N=257, N=256

Argentina		
De Paula, A.C.F	Director of the Hosp.	Gastros. e Hospital [illegible]
Kuhan, S.	Chief of Gastroentero	P[illegible] Hospital, [illegible]
Segal, J.E.	Chief of Gastroentero	[illegible] Hospital, Bue[illegible]
Australia		
Coulston, K.J.	Specialist in [illegible]	[illegible] General Hospital, Sydney
Mansky, J.	Gastroenterology	[illegible] Henry's Hospital, Melbourne
Piper, D.W.	Visiting Medical Officer	[illegible] North Shore Hospital, St. Leonards
Shearman, R.C.	Chairman, Joint [illegible] Medicine	[illegible] Adelaide Hospital, Adelaide
Austria		
Mentschel, E.	Internist	Lainz Hospital, Vienna
Reichel, W.	Director of Radiology	Rudolfsheimer Hospital, Vienna
Schatze, E.	Specialist in Internal Medicine	Lainz Hospital, Vienna
Brazil		
Raffanelli, A.	Professor	Medical School of Sao Paulo
Castro L.	Gastroenterologist	Federal University of Minas [illegible] Horizonte
Canada		
Archambault, A.	Head of Gastroenterology	Montreal General Hospital, Montreal
Hunt, R.H.	Head of Gastroenterology	McMaster [illegible] Department of Medicine, Hamilton
Marcon, N.E.	Head of Gastroenterology	[illegible]
Colombia		
Annote	Endoscopist, Gastroenterologist	Carrera 13 No. 90-63, Bogota
Denmark		
Rokkjaer, M.	Head Surgeon	Aarhus Amtssygehus Hospital, Aarhus
England		
Brown, P.	Consultant Physician	Royal Shrewsbury Hosp., Shrewsbury
Cockel, R.	Consultant Physician	Selly Oak Hospital, Birmingham
Cowan, R.E.	Consultant Physician	Essex County Hospital, Colchester
Fairclough, P.D.	Consultant Physician	St. Bartholomew's Hospital, London
Garnham, J.C.	Endoscopist	Wexham Park Hospital, Slough
Levi, A.J.	Consultant Gastroenterologist	Northwick Park Hospital, Harrow
Record, C.O.	Consultant Physician	Royal Victoria Infirmary, Newcastle
Sircus, W.	Consultant Physician	[illegible] Hospital, London
Finland		
Kerr Talman, O.	Chief of Gastroenterology	University Central Hosp. Tampere
Salesburg, M.P.	Chief, Gastroenterology	University Central Hosp. Helsinki
France		
Caravon, P.	Head of Gastroenterology	Centre Hosp. Regional, Besancon
Chaput, J.	Head of Gastroenterology	Hospital Antoine Beclere, Clamart
Ferrier, J.P.	Dept. Head, Gastroenterology	Hospital Jean Verdier, Bondy
Paris, J.C.	Dept. Head, Gastroenterology	Centre Hospitalier Regional, Lille
Ribet, A.	Dept. Head, Gastroenterology	[illegible] Hospital, [illegible] Toulouse
Germany		
Baumann, H.G.	Gastroenterologist	Bethanien Hospital, Hamburg
[illegible]sch, G.	Head, Dept. Gastroenterology	District Hospital Rastatt, Eichstaett
Hinderer, S.E.	Professor of Gastroenterology	Medical University Poliklinik, Bonn
Ottenjann, P.	Head of Internal Medicine	Municipal Hosp. Rue Neuberger, Munich
Pau[illegible], F.	Head of Medical Clinic II	Klinik Ingolstadt, Ingolstadt/Donau
Scholten, T.	Assistant Professor Gastroenterology	Med. Klinik u. Poliklinik University Duesseldorf
Schuetz, E.	Internist/Gastroenterologist	Gastroenterology-Proktolog. Regensburg
Seifert, E.	Head of Gastroenterology	Municipal Hospital Kemperhof, Koblenz
Simon, R.	Specialist for Gastroenterology	Medical University Klinik, Heidelburg
Stadelmann, O.	Head of Dept. of Gastro-	Chd. of Medical Klinik II, Fuerth
Holland		
Kattner, H.	Internist	Gasthuis Middelburg, Middelburg
Wesdorp, I.C.E.	Gastroenterologist	Andreas Hospital, Amsterdam
Ireland		
Crowe, J.	Gastroenterologist	Mater Misericordiae Hospital, Dublin
Gleeson, F.	Consultant Physician, Lecturer	James Connolly Memorial Hosp., Dublin
Weir, D.G.	Consultant Gastroenterologist	St. James' Hospital, Dublin
Italy		
Bauffoni, A.	Surgeon, Lecturer	Hospital Generale Provinciale
Barbara, L.	Director of Gastroenterology	Hospital Sant Orsola, Bologna
Bianchi-Porro, G.	Director of Gastroenterology	Hospital S. Carlo, Milan
Blasi, A.	Director of Gastroenterology	Hospital Vittorio Emanuele II, Catania
Carotenuto, F.	Head Surgeon	Municipal Hospital of Assisi,
Chelli, M.	Chief Dept. of Gastroenterology	Hospital S. Martino, Genova
Dal Monte, P.R.	Head Gastroenterologist	Hospital Bellaria, Bologna
Francavilla, A.	Head Physician	Cattedra di Malattie Apparato Digerent, Bari
Matarazzo, P.F.	Assistant Surgeon	Municipal Hospital of Parma,
Mazzacca, G.	Div. of Gastroenterology	School of Medicine, Naples
Pauluzi, P.	Gastroenterologist	II Clinical Medica University di Roma
Speranza, V.	Head of Surgical Clinic	II Clinical Chirurgica University degli Studi di Roma
Totti, F.	Head Surgeon	Municipal Hospital of Subiaco
Vagni, V.	Consultant Endoscopist	Municipal Hospital, Castellana
Verme, G.	Head Physician	Hospital Molinette, Torino
Mexico		
Villalobos, J.	Head of Dept. of Gastroenterogy	National Institute of Nutrition, Mexico, D.F.
New Zealand		
Yeomen-Jones C.	Associate Professor	Auckland Med. School, Auckland
Norway		
Fausa, O.	Head of Dept. of Gastro-enterology	Rikt Hospital, Oslo
South Africa		
Dantzwitz, M.D.	Head, Medical Gastroenterology	Johannesburg Hosp., Parktown
Marss, I.N.	Head, Gastro-intestinal Clinic	Groote Schuur Hospital,
Sweden		
Mradsky, M.	Chief of Gastroenterology Unit	Falu Hospital, Falun

(2) Exclusions from analysis of effectiveness: the number of patients excluded from analysis of healing because of protocol violations (table 30) was gratifyingly small, amounting to a total of 5%. Even the numbers lost from analysis because of absence of data on pain and global response (table 31) left a sufficiently large data base for meaningful analysis.

TABLE 30

Exclusions from Analysis of Effectiveness

Protocol Violation	Famotidine 40 HS	Famotidine 20 BID	Famotidine 40 BID	Ranitidine 150 BID	Total
Concomitant Drug	7	2	5	5	19
Initial Endoscopy or Ulcer Size Out of Range	5	6	3	4	18
Prior Surgery	1	0	1	0	2
Uncooperative Patient	2	4	2	4	12
TOTAL	15	12	11	13	51

TABLE 31

Number of Patients Omitted From Analysis of Effectiveness

	Famotidine 40 HS N=255			Famotidine 20 BID N=250			Famotidine 40 BID N=258			Ranitidine 150 BID N=259		
	WK 2	WK 4	WK 8	WK 2	WK 4	WK 8	WK 2	WK 4	WK 8	WK 2	WK 4	WK 8
Protocol Violators	15	15	15	12	12	12	11	11	11	13	13	13
No Day/Night Pain Data	22	21	20	20	17	20	18	17	18	21	19	19
No Global Response Data	44	23	23	37	16	17	39	18	18	40	18	18
NUMBER EVALUABLE												
Ulcer Healing	240	240	240	247	247	247	247	247	247	246	246	246
Day/Night Pain	230	234	235	239	240	239	240	241	240	238	240	240
Global Response	211	232	232	222	243	241	219	240	240	219	241	241

(3) Safety

(a) Vital signs (table 32): changes during treatment from baseline value were statistically significant for some or all of the treatments, but none of the changes were of clinical concern.

TABLE 32

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE	COMMENTS
Weight (kg)	40 HS	244	68.5	68.8	0.3	Increase for
	20 BID	250	69.0	69.0	0.0	each treatment
	40 BID	247	69.8	70.0	0.2	(p 0.01)
	Ranit	249	69.3	69.7	0.4	
Pulse	40 HS	235	75.0	74.0	-1.0	40 BID lower
	20 BID	248	75.2	74.6	-0.6	than 40 HS
	40 BID	240	73.6	73.4	-0.2	and 20 BID
	Ranit	242	74.4	74.0	-0.4	(p 0.5)
Systolic BP (mmHg)	40 HS	238	126.0	124.7	-1.3	No
	20 BID	249	126.9	126.5	-0.4	significant
	40 BID	241	126.1	125.6	-0.5	differences
	Ranit	244	126.8	125.7	-1.2	
Diastolic BP (mmHg)	40 HS	238	79.8	78.5	-1.1	40 HS and
	20 BID	249	79.6	79.1	-0.5	40 BID
	40 BID	241	79.6	78.6	-1.0	decreased
	Ranit	243	79.3	78.7	-0.6	p 0.05

(b) Clinical adverse events: adverse symptoms occurring with an incidence of 1.5% or more in at least one of the treatment groups (table 33) were primarily in the central nervous system (CNS) (famotidine 6%, ranitidine 8%) and the gastrointestinal (GI) system (famotidine 4%, ranitidine 5%). The most common CNS symptom, headache, occurred in 4% on both famotidine and ranitidine. The incidence of the most common GI symptom, diarrhea, was 1.3% on famotidine, 1.9% on ranitidine. The adverse experiences were considered serious in only 2/772 (0.2%) of patients receiving famotidine, 3/259 (1.2%) of those receiving ranitidine. Very few of the adverse symptoms were drug-related; e.g. the incidence of withdrawal of patients because of adverse experiences (table 34) was very low. Moreover such events as hemorrhage, development of a gastric ulcer or perforation of a duodenal ulcer are more appropriately classified as failures of therapy than as adverse drug effects.

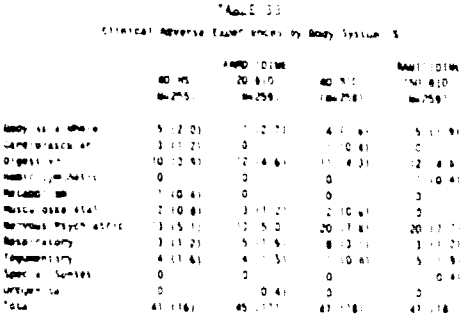


TABLE 34

Patients Withdrawn Due To Adverse Experience

TREATMENT GROUP	AN	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	TOTAL POSSIBLY/ PROBABLY
Famotidine 40 HS	172	Abdominal pain	Severe	Probably not[4]	
		Eructation	Severe	Probably not	
	42	Diarrhea	Severe	Possibly	
	540	Headache	Severe	Possibly	
	590	G.I. bleeding	Severe	Definitely not	
	1055	Gastric ulcer	Mild	Probably not	6/255 (2.4%)
Famotidine 20 BID	759	Gastric ulcer	Mild	Probably not	
	1130	Perforated duodenal ulcer	Moderate	Probably not	2/259 (0.7%)
Famotidine 40 BID	368	Pain, generalized	Severe	Possibly	
	465	Anorexia	Severe	Definitely	
		Anxiety	Severe	Definitely	
		Headache	Severe	Definitely	3/258 (0.8%)
Ranitidine 150 BID	52	Lung cancer	Severe	Definitely not	
	147	Diarrhea	Severe	Probably	
	721	Depression	Moderate	Possibly	
		Agitation	Moderate	Possibly	
		Concentration loss	Moderate	Possibly	
		Malaise	Moderate	Possibly	3/259 (1%)

4 "Probably not" = "Possibly yes"

(c) Laboratory adverse events were infrequent (table 35), occurring in approximately 4% of patients in each group. No patient was withdrawn because of an abnormal laboratory finding.

TABLE 35

Laboratory adverse events/number at risk

	Famotidine 40 HS (N=255)	Famotidine 20 BID (N=259)	Famotidine 40 BID (N=258)	Ranitidine 150 BID (N=259)
Hematology	6/235	5/242	6/231	3/236
Liver Function	2/229	3/230	3/230	9/234
Renal Function	0/143	0/150	1/140	1/143
Metabolic	0/100	0/104	1/95	0/99
Urogenital	1/235	0/242	2/231	1/236

(4) Effectiveness

(a) Incidence of healing: the sponsor displays the data for incidence of healing at 2, 4, and 8 weeks in the conventional manner (table 36) in which the 2-week endoscopy could be as late as 18 days, the 4-week endoscopy as late as 34 days, and the 8-week endoscopy as late 64 days. The resulting numbers do not correctly reflect the interval of healing, as illustrated by the tabulation in which the incidence of healing is displayed by actual weeks (table 37) As in the U.S. trial, it is clear that the optimal interval to endoscope patients on treatment is 5 weeks. By both methods of calculation, the 20 mg b.i.d. and 40 mg b.i.d. doses of famotidine are more effective at 2, 4 and 8 weeks than the sponsor's proposed dose of 40 mg h.s.

TABLE 36

Cumulative Number Healed/Number Evaluable (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=240	Famotidine 20 BID N=247	Famotidine 40 BID N=247	Ranitidine 150 BID N=246
2 (Days [illegible]-18)	82 (34)	94 (38)	[illegible] (44)	96 (39)
4 (Days 19-34)	164 (68)	191 [illegible] *	20[illegible] (8[illegible]) *	186 (7[illegible])
8 (Days 35-64)	210 (88)	228 (92)	22[illegible] [illegible]	222 (90)
Beyond week 8 (Days 6[illegible]-[illegible])	21[illegible] (88)	231 (94) *	23[illegible] (94) *	[illegible] (9[illegible])

* Significantly higher than famotidine 40 h.s., p< 05

TABLE 37

Cumulative Number Healed (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=240	Famotidine 20 BID N=247	Famotidine 40 BID N=247	Ranitidine 150 BID N=246
Week 1 (Days 2-8)*	0 (0)	0 (0)	0 (0)	0 (0)
Week 2 (Days 9-15)	62 (26)	72 (29)	84 (34)	72 (29)
Week 3 (Days 16-22)	87 (36)	99 (40)	114 (46)	100 (41)
Week 4 (Days 23-29)	141 (59)	165 (67)	173 (70)	163 (66)
Week 5 (Days 30-36)	169 (70)	194 (79)	203 (82)	191 (78)
Week 6 (Days 37-43)	170 (71)	197 (80)	206 (83)	192 (78)
Week 7 (Days 44-50)	170 (71)	197 (80)	206 (83)	193 (78)
Week 8 (Days 51-57)	186 (78)	211 (85)	219 (89)	207 (84)

* Day 1 was the day of the baseline evaluation. Patients started taking drug at bedtime on day 1. All weekly day ranges start with day 2

(b) The incidence of healing as reported by those investigators who had at least 20 patients (table 38) shows comparatively little treatment by investigator interaction at the important intervals (weeks 4 and 8) except for those intervals where the investigators had too few patients to make the differences meaningful. It is curious but inexplicible that in the sponsor's proposed dose (40 mg h.s.) for the short-term treatment, the total incidence of healing reported by the investigators with 20 or more patients was much higher (85%) than that of all of the rest of the investigators combined (63%). By whatever method the data are calculated, at week 2 and more importantly at week 4, the incidence of healing is higher with ranitidine b.i.d. than with the sponsor's recommended dose of famotidine 40 mg h.s.

TABLE [illegible]

[illegible]

Investigator	City	N	Wk 2	Wk 4	Wk 8	N	Wk 2	Wk 4	Wk 8	N	Wk 2	Wk 4	Wk 8	N	Wk 2	Wk 4	Wk 8
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SUBTOTAL		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TOTAL		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible] investigators combined

(c) Relief of pain: the percentage of patients relieved of day pain (figure 39) and night pain (figure 40) was the same at all recorded intervals for all 4 treatments. Contrary to what one might expect, time to relief of day pain (table 39) was no shorter in patients whose pain was mild on entry than in those with moderate to severe pain on entry, except for patients receiving ranitidine in whom the more severe the pain, the longer the time to relief. Time to relief of night pain was, however, more rapid with all treatments in patients with initially mild pain than in those with moderate or severe pain.

Figure 39

PERCENTAGE OF PATIENTS WITH NO DAY PAIN

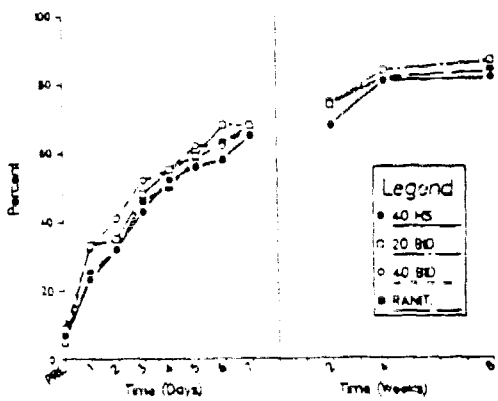


Figure 40

PERCENTAGE OF PATIENTS WITH NO NIGHT PAIN

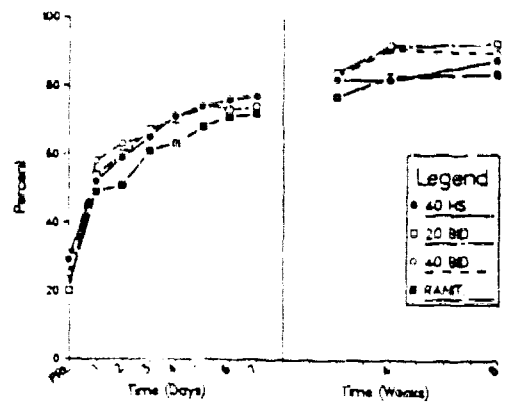


TABLE 39

Incidence of, and Median Time to Relief of Pain (Days)

	FAMOTIDINE 40 HS (n = 260)	FAMOTIDINE 20 BID (n = 247)	FAMOTIDINE 40 BID (n = 247)	RANITIDINE 150 BID (n = 246)
Day Pain				
Incidence (%)	224 (93)	235 (95)	224 (9	234 (95)
Baseline: absent	1.0 (n = 16)	1.0 (n = 21)	1.0 (n = 23)	2.5 (n = 6)
Mild	11.0 (n = 54)	6.0 (n = 49)	5.0 (n = 53)	4.5 (n = 62)
Moderate	7.0 (n = 119)	6.0 (n = 122)	7.0 (n = 108)	7.0 (n = 100)
Severe	7.0 (n = 51)	7.0 (n = 35)	7.0 (n = 40)	18.0 (n = 12)
Total	7.0 (n = 240)	6.0 (n = 247)	6.0 (n = 247)*	7.0 (n = 246)
Night Pain				
Incidence (%)	(1) (1)	(9) (80)	(85) (9	(9) (8
Baseline: None	1.0 (n = 49)	0 (n = 50)	1.0 (n = 42)	2 (n = 49)
Mild	3.0 (n = 31)	3.0 (n = 50)	3.0 (n = 1)	3.0 (n = 1)
Moderate	5.0 (n = 80)	5.5 (n = 88)	6.0 (n = 92)	4.0 (n = 85)
Severe	7.0 (n = 58)	6.0 (n = 60)	7.0 (n = 55)	5.0 (n = 9
Total	3.5 (n = 240)	3.0 (n = 247)**	3.0 (n = 247)**	5.0 (n = 246

Some patients had no pain at baseline but had pain at one or more subsequent timepoints

** Significantly shorter than the ranitidine group ($p < .01$)

* Significantly shorter than the famotidine 40 HS group ($p < .05$)

(d) Antacid consumption: the percentage of patients receiving antacid therapy was consistently greater with ranitidine than with famotidine during the first 4 weeks, after which very few patients were still taking antacids (figure 41). During the first 2 weeks the mean number of days in which antacid therapy was taken was significantly greater with the patients receiving ranitidine than with those receiving the 2 b.i.d. doses of famotidine but the differences amount to only a fraction of a day (table 40). No difference emerged between ranitidine and the 40 h.s. dose of famotidine.

Figure 41
Percentage of Patients Receiving Antacid Therapy

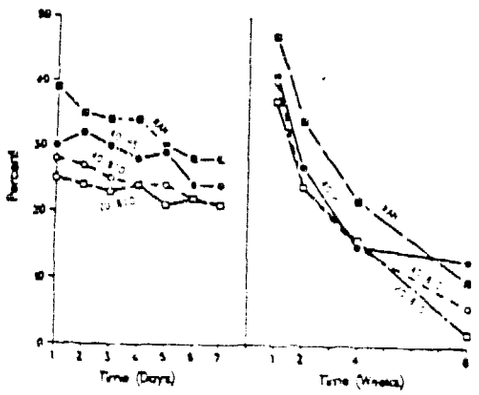


TABLE 40
Mean Days of Antacid Therapy, Mean ± Standard Deviation

WEEK	FAMOTIDINE 40 HS N	FAMOTIDINE 40 HS MEAN	FAMOTIDINE 20 BID N	FAMOTIDINE 20 BID MEAN	FAMOTIDINE 40 BID N	FAMOTIDINE 40 BID MEAN	RANITIDINE 150 BID N	RANITIDINE 150 BID MEAN	NUMBER OF DAYS DIFFERENCE BETWEEN 40 [illegible] & RANITIDI
1	241	2.0 ± 2.7	250	1.6 ± [illegible]***	249	1.7 ± 2.6*	247	2.3 ± 3.0	[illegible]
2	227	1.3 ± 2.4	239	0.9 ± [illegible]**	237	1.1 ± 2.3*	237	1.6 ± 2.7	[illegible]
4	132	0.8 ± 2.0	140	1.0 ± [illegible]	133	0.7 ± 1.9	129	1.2 ± 2.5	[illegible]
8	51	0.7 ± [illegible]	41	0.20 ± [illegible]	28	0.5 ± [illegible]	40	0.7 ± 2.1	[illegible]

***, ** Significantly [illegible]erent from the ranitidine group (p [illegible]05, p [illegible]01, respectively).
Significantly [illegible]erent from the 40 HS group (p [illegible]05).
Mean Number of [illegible]s of antacid therapy is the [illegible]-day period ending the relative day of the pain measurements taken at this week. Other [illegible] patients have no pain measurements; numbers may [illegible].
N Number of patients evaluated

e. Summary: 1,031 patients were entered into a multicenter trial of 3 doses of famotidine (40 mg h.s., 20 mg b.i.d. and 40 mg b.i.d.) vs ranitidine 150 mg b.i.d. in the short-term treatment of duodenal ulcer. The incidence of healing was:

WK	Fam 40 HS	Fam 20 BID	Fam 40 BID	Ran 50 BID
4	68%	77%	81%	76%
8	87%	92%	92%	90%

Thus the incidence of healing with ranitidine at the important 4 week follow-up was of the same order as that with famotidine 20 mg b.i.d. and 40 mg b.i.d. but was higher than with the sponsor's recommended dose of 40 mg h.s. The percentage of patients relieved of both day and night pain was in the neighborhood of 60% at the end of the first week and 80% at the end of 8 weeks with all 4 treatments. The time to relief of day pain in famotidine-treated patients was generally not shorter when the pain was initially mild than when it was moderate or severe, averaging 6-7 days. In patients receiving ranitidine the average time to relief of severe pain was 18 days contrasted with 4.5 days for mild pain. The average number of days in which patients took antacids differed by a fraction of a day among the 4 treatment groups, a clinically meaningless difference. The percentage of patients receiving antacids during the first 2 weeks of treatment was significantly less in patients receiving famotidine 20 mg b.i.d. than in those receiving ranitidine, but at no time point was there an advantage of the sponsor's recommended dose (40 mg h.s.) over ranitidine in the number of patients requiring concomitant antacid therapy. The incidence of drug-related adverse events requiring withdrawal of patients from famotidine treatment was less than 1%.

An interesting difference between the conduct of the U.S. and foreign trials in the short-term treatment of duodenal ulcer is that twice as many U.S. investigators contributed 10 or fewer patients, while twice as many foreign investigators contributed 11 or more patients. It would be instructive to know whether this difference is because the foreign investigators had more time to complete the assigned number of patients, had more patients available to them, are more persuasive in convincing patients to enter clinical trials, or whether patients are more easily persuaded to participate when the control substance is a drug of known effectiveness rather than a placebo.

2. Protocol No. 503-00

a. Title of study: A double-blind study in out-patients to compare famotidine with placebo in the long-term maintenance treatment of duodenal ulcer (weeks 1-24).

b. Design of study: the procedure was identical with that of the U.S. multi-center trial of prevention of recurrence except that only 1 dose of famotidine, 20 mg h.s., was compared with placebo.

c. Investigators: 64 of the 68 investigators listed in the short-term trial participated.

d. Results

(1) Comparability of patient groups (table 41): there were 306 patients on famotidine, 339 on placebo. The groups were comparable in all relevant respects.

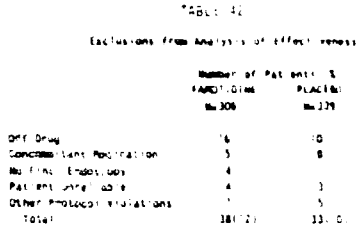
TABLE 41

Comparability of Treatment Groups

	Famotidine 20 mg h.s. (N=306)[a]	Placebo (N=339)[a]
Age (years), Mean	43.5	43.9
Sex		
Males	222 (73%)	237 (69%)
Females	84 (27%)	102 (30%)
Treatment in the Acute Study		
Famotidine 40 mg	76 (25%)	[illegible]
Famotidine 20 BID	61 (20%)	[illegible]
Famotidine 40 BID	82 (26%)	[illegible]
Ranitidine 300 mg h.s.	78 (25%)	[illegible]
Ulcer Healed in the Acute Study		
Week 2	33 (64%)	29 (59%)
Week 4	28 (42%)	[illegible]
Week 8 or later	43 (7%)	[illegible]
[illegible][b]	68 (55%)	[illegible]
[illegible][b]	[illegible]	[illegible]
Initial ulcer size[b] (cm), Mean	1.9	1.90
Number of ulcers[b]		
One	276 (90%)	304 (90%)
Two or more	29 (9%)	33 (9%)
Age at first ulcer[b] (years)		
Mean	38.2	38.0
Median	35.0	36.0
Duration of ulcer disease[b] (years)		
Mean	5.6	5.7
Median	3.0	3.0
Ulcer history[b]		
None	67 (22%)	98 (29%)
One Prev ous Episode	83 (27%)	88 (26%)
Multiple Previous Episodes	135 (46%)	151 (45%)
Race		
Caucasian	270 (88%)	311 (92%)
Black	8 (3%)	7 (2%)
Hispanic	5 (2%)	7 (2%)
Other	23 (7%)	14 (4%)
Other Pathology in the Esophagus	19 (6%)	23 (7%)
Other Pathology in the Stomach	30 (10%)	37 (9%)
Other Pathology in the Duodenum	160 (54%)	191 (57%)

[a]Maximum counts; some patients had no information for some variables
[b]Status at the beginning of the short term study

(2) Exclusions from analysis of effectiveness (table 42): 38/306 (12%) of patients receiving famotidine and 33/309 (10%) of patients receiving placebo were excluded, primarily because of various protocol violations, the most common of which were (a) failure to take the drug as prescribed and (b) taking forbidden concomitant medications. The percentage lost was in the same range as that in the U.S. trial.



(3) Safety

(a) Vital signs: other than an increase in body weight, of no clinical import, in patients receiving famotidine compared with patients receiving placebo, there was no difference between the treatments with regard to change from baseline or difference from each other.

(b) Clinical adverse experiences (table 43) occurred with somewhat higher frequency in patients on famotidine (25%) than on placebo (19%); the difference is not statistically significant. Headache, the most common CNS symptom, occurred with equal frequency in the 2 groups (famotidine 2.6%, placebo 2.9%).

TABLE 43

Number of Patients with Adverse Experiences (%)

BODY SYSTEM	Famotidine 20 MG N = 306	Placebo N = 339
Central Nervous	16 (5.2)	20 (5.9)
Cardiovascular	3 (1.0)	1 (0.3)
Digestive	14 (4.6)	21 (6.2)
Respiratory	21 (6.9)	8 (2.4)
Tegumentary	7 (2.3)	6 (1.8)
Musculoskeletal	6 (2.0)	2 (0.6)
Heme/Lymphatic	1 (0.3)	0
Special Senses	4 (1.3)	4 (1.2)
Urogenital	4 (1.3)	2 (0.6)
TOTAL	76 (25)	64 (19)

Symptoms evaluated by the investigator as possibly, probably or definitely drug-related were recorded in 5/306 (1.6%) of patients receiving famotidine, 9/339 (2.7%) of patients receiving placebo. The only really troublesome adverse clinical event in patients receiving famotidine was alopecia in one patient; however, it was also reported in one patient receiving placebo. Among patients 65 years of age or older clinical adverse experiences occurred in 8/18 (44%) on famotidine, 5/17 (29%) on placebo; however, the adverse experiences reported in this age group appeared to be related not to a drug-effect but rather to diseases associated with advancing age such as myocardial infarction, traumatic arthropathy, insomnia, Parkinson's disease and neoplasia. This is a reflection of the FDA requirement that all adverse events occurring during a clinical trial be reported; for example injury or death from a gunshot wound or a traffic accident while a patient is in a clinical trial must be reported as an adverse event which it obviously is, but which equally obviously has nothing to do with the treatment. Since such events could occur with equal frequency in patients receiving a drug as in those receiving a placebo, it is not surprising that, in a clinical trial of a drug as safe as famotidine, the percent of patients withdrawn because of adverse experiences in this trial was the same with famotidine, 9/306 as with placebo, 8/339 (2.4%). Interpretation of these numbers is complicated by the fact that investigators differ in their assessments of possibly/probably drug-related effects. These differences are illustrated in the 8 patients in whom serious adverse events were reported:

A 50 year old man receiving famotidine experienced 2 episodes of hematemesis and hematochezia on day 34. Endoscopy 2 days later revealed a 2.0 cm duodenal ulcer with signs of bleeding. Following gastric resection the patient had an uneventful recovery. The investigator assessed this occurrence as probably not drug-related.

The duodenal ulcer in a 50 year old man with tarry stools on entry into the short-term trial healed complete on ranitidine; the patient was enrolled in the maintenance study on famotidine. On day 85 endoscopy revealed hemorrhagic gastritis. On day 123 the patient reported fulness; endoscopy showed bleeding varices in the gastric fundus. Carcinoma of the pancreas was suspected and was confirmed at surgery on the following day. The investigator's opinion was that this was probably not a drug-related event.

A 70 year old man was hospitalized because of chest pain on day 8 of treatment with famotidine. There were no significant changes in the ECG; enzyme levels were not raised. After discharge, medication was restarted. On day 77 the patient again experienced chest pain and was withdrawn from the study. He later underwent surgery for pneumothorax. The investigator thought that this occurrence was probably not drug related.

A 48 year old man experienced asthenia, headache and dizziness during treatment with ranitidine in the short-term study. In the maintenance study he was randomized to receive famotidine. On day 36 he was withdrawn from the study because of severe asthenia and an ALAT of 592. A diagnosis of hepatitis B was established. Eight months later the ALAT was still elevated (450) but no clinical symptoms were present. The investigator concluded that the hepatitis was definitely not drug-related.

A 71 year old man taking several drugs for peripheral vascular disease was randomized to the famotidine treatment group. On day 70 he suffered myocardial infarction and died within 2 hours. The investigator concluded that this was definitely not drug-related.

A 69 year old man with a history of perforated duodenal ulcer complicated by a right subphrenic abscess was entered into the maintenance trial despite the fact that after 4 weeks of treatment with famotidine 40 mg h.s. in the short-term trial his abdominal pain had not improved and endoscopic examination was not possible because of pyloric deformity. On day 10 the patient was hospitalized for hematemesis and was found to have bronchial carcinoma metastasic to the liver. The investigator concluded that this occurrence was definitely not drug-related.

A 59 year old woman experienced a myocardial infarction on day 24 of treatment with placebo. She subsequently recovered. The investigator assessed this experience as probably not drug-related.

A 56 year old man receiving placebo was found on day 25 to have cancer of colon. The investigator believed that this was definitely not drug-related.

It is obvious from the above summaries that these serious clinical adverse experiences were not drug-related, even though the assessment "probably not" is tantamount to "possibly yes."

(c) Laboratory adverse experiences (table 44): the only noteworthy observation was the occurrence of abnormal results of tests of hepatic injury in 15/255 (6%) of patients receiving famotidine vs 0/271 with placebo. If these numbers are correct, famotidine will bear watching for possible hepatotoxicity; however, none of the changes were serious and only one patient was withdrawn from the study because of a suspect laboratory value. Among the 18 patients 65 years or older receiving famotidine there were no laboratory adverse events.

TABLE 44

Laboratory Adverse Events/Number at Risk

	Famotidine 20 HS N = 306	Placebo N = 339
Hematologic	11/256	10/269
Renal Function	1/151	3/158
Hepatic	15/255	0/271
Metabolic	1/110	2/116
Urogenital	0/258	1/269

(4) Effectiveness

(a) Prevention of recurrence: famotidine significantly decreased the rate and the incidence of recurrence of duodenal ulcer (table 45) compared to placebo. In patients receiving placebo the incidence of recurrence within the first 4 months was an astonishing 60% vs 20% of those receiving famotidine. Data extending to almost 9 months put the incidence of recurrence with placebo (74%) at more than twice that with famotidine; while this is a highly significant difference favoring famotidine, it is far from an impressive achievement, especially since in patients treated with famotidine there was a substantial increase in recurrences from the end of 6 months onward.

TABLE 45

Number of Patients Who Relapsed (%)*
(Life Table Rate)

Months, Day Range of Treatment	FAMOTIDINE 20 HS (N = 306)	PLACEBO (N = 339)
Month 1 Days 1-28	3 (1.0)	21 (6.)
Month 2 Days 29-56	9 (3.)	60 (19.)
Month 3 Days 57-84	24 (9.)	103 (33.)
Month 4 Days 85-112	50 (19.)	185 (62.)
Month 5 Days 113-140	55 (21.)	193 (66.)
Month 6 Days 141-168	58 (22.)	195 (67.)
After Month 6 Days (169-245)	62 (24.)	215 (74.)

*All Patients Treated Analysis

(b) Relief of pain (table 46): as would be expected from the data on recurrence of ulcers, famotidine was much more effective than placebo in preventing recurrence of ulcer pain. Since patients eligible for admission to the trial were those in whom the ulcer had healed during short-term treatment, the incidence of moderate to severe pain at baseline was negligible. However, the proportion of patients experiencing moderate to severe pain by the end of the study was clearly much greater in patients on placebo than in those on famotidine.

TABLE 46

Distribution of Day and Night Pain

Severity of Pain Baseline	Severity of Pain End of Study	Day Pain Famotidine	Day Pain Placebo	Night Pain Famotidine	Night Pain Placebo
None	None	161	94	192	42
None	Mild	27	56	22	44
None	Mod./Severe	23	115	13	98
Mild	None	26	15	21	6
Mild	Mild	11	7	3	5
Mild	Mod./Severe	8	12	3	3
Mod./Severe	None	2	0	4	2
Mod./Severe	Mild	1	1	0	0
Mod./Severe	Mod./Severe	0	1	0	1

Significant difference between treatments, p<.01 in favor of famotidine for both day pain and night pain.

(c) Antacid consumption: the proportion of patients who took antacids at any time during the trial was significantly higher in patients on placebo (49%) than in those on famotidine (33%), p 0.01. However, the number of doses taken is not reported.

e. Summary: in a multicenter double-blind placebo controlled trial of famotidine 20 mg h.s. (306 patients) vs placebo (339 patients), famotidine was statistically significantly more effective than placebo over a period of 6-9 months in preventing recurrence of duodenal ulcer, relapse of symptoms and requirement for concomitant antacid therapy. Nevertheless, the incidence of recurrence with famotidine, 22% at the end of 6 months, 34% at the end of an additional 3 months, suggests that by the end of a year the incidence of recurrence may well be higher than the 25-35% incidence reported in clinical trials of other drugs.

3. Study No. 5007

a. Title of study: Comparison of famotidine vs placebo in the short-term treatment of gastric ulcer.

b. Design of study: patients with clinical symptoms and endoscopic evidence of a gastric ulcer measuring 0.5-2.5 cm were allocated randomly to receive either famotidine 40 mg or matching placebo at bedtime. Each patient received a bottle of antacid tablets to be taken only if additional symptomatic relief was required. The maximum number of tablets allowed per day had a neutralizing capacity of 88 mEq/day.

Exclusions and procedures at the initial (screening) visit were the same as in the protocol for short-term treatment of duodenal ulcer. Assessment of clinical symptoms and endoscopy were performed at weeks 4, 6 and 8 unless complete healing of the ulcer was demonstrated at the previous visit. At each visit patients were given take-home cards to record day and night pain, number of antacid tablets taken and any adverse experiences. Adverse symptoms and laboratory events were evaluated by the investigator.

An ulcer was considered healed if there was complete epithelization of the crater, regardless of the emergence or persistence of gastritis or erosions. A biopsy was performed at the initial visit, and, at the discretion of the investigator, at subsequent visits, to rule out gastric carcinoma.

Day and night pain and overall therapeutic responses were scored using the same grading system described above in the foreign short-term trial of healing of duodenal ulcer.

Investigators (table 47): the 44 investigators from 14 countries are all qualified by training and experience to conduct a clinical trial of this type.

Table 47

Country/Name	Affiliation	Location
Argentina		
A. DePaula, A.O.F.	Director of the Hospital	Ramos Mejia Hospital, Buenos Aires
Roman, S.	Chief of Gastroenterology Dept.	Piravana Hospital, Buenos Aires
Vegal, J.E.	Chief of Gastroenterology Dept.	Durand Hospital, Buenos Aires
Austria		
Hanusch, E.	Internist	Hanusch Hospital, Vienna
Reichel, W.	Director of Endoscopical Ambulance	Wilhelminen Hospital, Vienna
Schultze, K.	Specialist in Internal Medicine	Hanusch Hospital, Vienna
Brazil		
Castro, L.	Gastroenterologist	Federal University of Minas
Vilela, M.P.	Gastroenterologist	Hospital Sao Paulo
Canada		
Archambault, A.	Head of Gastroenterology	Maisonneuve-Rosemont, Hospital Montreal
Marcon, N.W.	Head of Gastroenterology	The Wellesley Hospital, Toronto
Colombia		
Aponte, E.	Endoscopist/Gastroenterologist	Carrera 18 No. 80-67, Bogota
Denmark		
Rokkjaer, M.	Head Surgeon	Arhus Council Hospital, Arhus
Holland		
Peltner, H.	Internist	Gasthuis Middelburg, Middelburg
Van Benteu	Gastroenterologist	De Stadsmaten Hospital, Enshede
Wesdorp, I.C.E.	Gastroenterologist	Andreas Hospital, Amsterdam
Italy		
Baglioni, A.	Surgeon, Lecturer	Hospital Generale, ... ciale, "SS Trinita", Sora
Barbara, L.	Director of Gastroenterology	Hospital Sant'Orsola, Bologna
Bianchi-Porro, G.	Director of Gastroenterology	Hospital L. Sacco, Milan
Blasi, A.	Director of Gastroenterology	Hospital Vittorio, Emanuele II, Catania
Carotenuto, F.	Head Surgeon	Municipal Hospital of Cassino
Cheli, R.	Chief of Gastroenterology	Hospital S. Martino, Genova
Dal Monte, P.R.	Head Gastroenterologist	Hospital Bellaria, Bologna
Francavilla, A.	Head of Gastroenterology	Cattedra de Malattie, Bari Apparato
Matarazzo, P.F.	Assistant Surgeon	Municipal Hospital of Formia
Mazzacca, G.	Division of Gastroenterology	School of Medicine, Naples
Paoluzi, P.	Gastroenterologist/Endoscopist	II Clinical Medica Universita
Sperenza, V.	Head of Surgical Clinic	VI Clinical Chirurgica University
Vagni, V.	Consultant Endoscopist, Lecturer	Municipal Hospital Castellana
Verme, G.	Professor, Head Physician	Hospital Molinette, Torino
Finland		
Pikkarainen, P.	Head of Gastroenterology	University Centre, Hospital, Kuopio
Koskela, T.	Physician	University Central Hospital, Oulu
France		
Paris, J.C.	Head of Gastroenterology	Centre Hospitalier Regional, Lille
Sarles, H.	Professor, Dept. Head	Hospital of Sante Marseille Marguerite
Germany		
Dammann, H.G.	Head of Gastroenterology	Bethanien Hospital, Hamburg
Jakob, G.	Head of Gastroenterology	District Hospital, Eichstaett
Miedemer, S.E.	Professor of Gastroenterology	Medical University Poliklinik, Bonn
Ottenjann, R.	Head of Dept. of Intern. Medicine	Municiple Hospital Mue
Paul, F.	Professor, Head of Medical Clinic II	Klinik Ingolstadt, Ingolstadt/Donau
Schuetz, E.	Internist/Gastroenterologist	Gastroenterology-Proctology, Regensburg
Simon, B.	Specialist for Gastroenterology	Medical University, Klinik, Heidelberg
Stadelmann, O.	Head of Gastroenterology	CNA d. Medical Klinik Fuerth
Mexico		
Villatoboos, J.	Head of Gastroenterology	National Institute of Nutrition, Mexico, D.F.
South Africa		
Minder, R.A.	Gastroenterologist	Johannesburg Hospital, Parktown
Mel, C.J.C.	Professor, Gastroenterologist	University Hospital, Bloemfontein
Sweden		
Hradsky, M.	Chief of Gastroenterology Unit	Falu Hospital, Falun

d. Results

(1) Comparability of the treatment groups (table 48): case report forms for 336 patients were available by the cut-off date of December 21, 1984, 167 randomized to famotidine, 169 to placebo; the 2 groups were comparable in all respects except that there was a significantly higher (p 0.01) proportion of drinkers among patients in the placebo group.

TABLE 48

Comparability of Treatment Groups

	Famotidine N = 167	Placebo N = 169
Age (yrs)		
Mean	52.2	51.5
Median	55.0	54.0
Sex		
Males	104	104
Females	63	65
Weight (kg)	66.3	66.2
Smoking	98 (59%)	104 (62%)
Alcohol	70* (42%)	100 (57%)
Initial Ulcer Size (cm)[a]		
Mean	1.15	1.00
Median	1.00	1.00
Number of Ulcers		
One	148 (89%)	159 (94%)
Two or more	19 (11%)	10 (6%)
Age at First Ulcer (yrs)		
Mean	48.2	47.2
Median	52.0	47.0
Duration of Ulcer Dis.(yrs)		
Mean	4.0	4.4
Median	0.0	0.0
Ulcer History		
None	85 (51%)	86 (51%)
Single	41 (25%)	37 (22%)
Multiple	41 (25%)	40 (24%)
Other pathology, Esophagus	13 (8%)	11 (7%)
Other pathology, Stomach	51 (31%)	61 (36%)
Other pathology, Duodenum	31 (19%)	29 (17%)

a For patients with more than one ulcer, this was the size of the largest ulcer

* Significantly different from the placebo group (p 0.01).

(2) Exclusions from analysis of effectiveness (table 49): 11% of the patients randomized to receive famotidine and 14% of those randomized to placebo were excluded for various protocol violations. These percentages are not excessive compared with numbers reported in other NDAs for studies of this type.

TABLE 49

Exclusions from analysis of effectiveness

Reasons	Famotidine N=167	Placebo N=169
Off drug	2	4
Ulcer 2.5 cm	5	3
Ulcer 0.5 cm	3	3
Cancer at entry	1	5
Concomitant medication	3	3
Endoscopy out of range	2	1
Other	2	5
Total (%)	18 (11)	24 (14)

(3) Safety

(a) Vital signs (table 50): the only change in vital signs after treatment was a clinically inconsequential mean weight gain of 0.4 kg in patients on famotidine.

TABLE 50

Effect of Treatment on Vital Signs (Means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE
Pulse rate	Famotidine	161	74.7	74.9	0.2
	Placebo	160	74.7	75.1	0.4
Systolic BP	Famotidine	161	133.0	131.8	-1.2
	Placebo	161	131.8	132.2	0.4
Diastolic BP (mmHg)	Famotidine	159	80.8	80.6	-0.2
	Placebo	159	80.3	81.5	1.2
Weight (kgs)	Famotidine	161	66.3	66.7	0.4##,*
	Placebo	162	66.2	66.1	-0.1

* Significant difference between treatment groups ($p < 0.05$).
Significant increase from baseline ($p < 0.01$).

(b) Adverse signs/symptoms were no more frequent among patients receiving famotidine than among those receiving placebo, totaling 13% of the patients entered in either group (table 51). The proportions considered by the investigators to be possibly/probably drug-related were also the same for each group (famotidine 7%, placebo 6%). The investigators considered withdrawals drug-related in 1 famotidine-treated patient (0.6%) and 5 placebo patients (3%) (table 52). Among the adverse reactions considered serious, 3 occurred in patients receiving famotidine, the first of which was a 55 year old man withdrawn from the study after 29 days of treatment after surgical removal of a melanoma of the skin, the second a 26 year old women withdrawn at the first follow-up visit because endoscopic biopsy revealed multiple granulomatous ulcers compatible with a diagnosis of Crohn's gastritis, the 3rd a 42 year old paraplegic male who had a pulmonary embolism 12 days after entering the trial. The one patient with a serious adverse clinical reaction in the placebo group was a 39 year old man in whom, because the ulcer had not healed at 8 weeks, a biopsy was performed and found to contain carcinoma. Obviously none of these reactions could by any stretch of the imagination be considered drug-related.

TABLE 51

Clinical Adverse Experiences By Body System (%)

	FAMOTIDINE N = 167	PLACEBO N = 169
Body as a whole	1 (0.6)	3 (1.8)
Cardiovascular	1 (0.6)	1 (0.6)
Central Nervous	1 (0.6)	1 (0.6)
Digestive	9 (5.4)	7 (4.1)
Integumentary	2 (1.2)	3 (1.8)
Metabolic/Nutritional	2 (1.2)	0 (0.0)
Lymphatic		
Musculoskeletal	1 (0.6)	2 (1.2)
Nervous and Psychiatric	5 (3.0)	4 (2.4)
Respiratory	5 (3.0)	4 (2.4)
Integumentary	2 (1.2)	2 (1.2)
Special Senses	1 (0.6)	0 (0.0)
Urogenital	3 (1.8)	2 (1.2)
Total	22 (13.2)	22 (13.0)

TABLE 52

Patients Withdrawn Due to Adverse Experience

TREATMENT GROUP	AN	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	TOTAL POSSIBLY PROBAB DEFINITELY
Famotidine 40 MS	39	Disorientation	Severe	Possibly	
		Muscular cramps	Severe	Probably	
		Sexual impotence	Severe	Probably	
	152	Acid regurgitation	Moderate	Definitely Not	
		Fullness	Moderate	Definitely Not	
	205	Skin melanoma	--	Definitely Not	
	293	Gastric granuloma	Severe	Definitely Not	
	310	Development of duodenal ulcer	Mild	Definitely Not	
	316	Pulmonary embolism	Severe	Definitely Not	
		Pneumonia	Severe	Definitely Not	3 (0.6%)
Placebo	63	Asthenia	Mild	Possibly	
	123	Abdominal discomfort	Severe	Definitely	
		Flatulence	Moderate	Definitely	
		Fullness	Severe	Definitely	
		Nausea	Severe	Definitely	
		Vomiting	Severe	Definitely	
	136	Headache	Severe	Probably	
		Nausea	Moderate	Possibly	
		Development of duodenal ulcers	--	Definitely Not	
	197	Nausea	Mild	Probably Not[a]	
		Duodenal ulcer	Moderate	Probably	
		Flatulence	Mild	Probably Not[a]	
		Cold	Mild	Definitely Not	
		Cough	Mild	Definitely Not	
		Fever	Moderate	Definitely Not	
	333	Vomiting	Moderate	Probably Not[a]	5 (1.5%)

[a]"Probably not" = "Probably"

(c) Laboratory adverse events: there were 5 abnormal laboratory reports in patients receiving famotidine, 6 in patients receiving placebo; none of these were serious or drug-related or necessitated withdrawal of the patients from the trial.

(4) Effectiveness

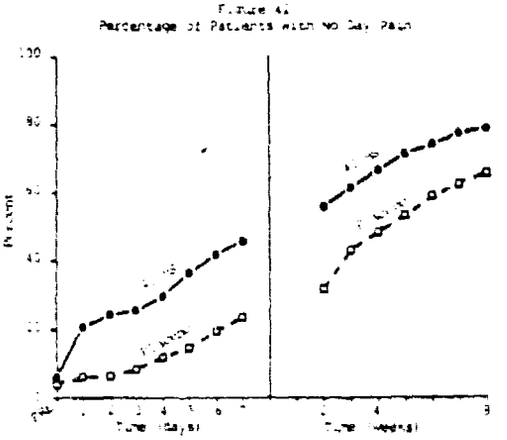
(a) Incidence of healing (table 53): the cumulative incidence of healing with famotidine was 45% at week 4, 62% at week 6, 77% at week 8, all statistically significantly superior to the incidence of healing in patients receiving placebo (30%, 44% and 51%) at the respective weeks.

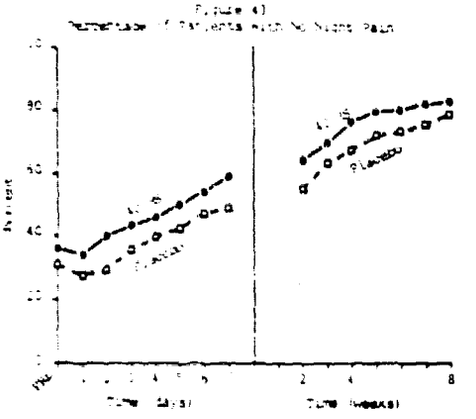
TABLE 53

Cumulative Number Healed/Number Entered (%)

Weeks	Endoscopic Range Days	Famotidine 40 mg bid	Placebo	p
4	28 to 34	75/165 (45)	50/165 (30)	<0.01
6	35 to 48	104/165 (62)	74/165 (44)	<0.01
8	50 to 64	128/165 (77)	86/165 (51)	<0.01
Later	After 64	131/165 (79)	88/165 (53)	<0.01

(b) Relief of pain: the proportion of patients relieved of day pain (figure 42) was clearly higher in those receiving famotidine at all intervals from the first day of treatment through the end of the 8th week. By the end of the first week day pain was relieved in some 40% of patients on famotidine vs 20% in patients on placebo; by the end of the study the difference in the proportion of patients without day pain had narrowed between the 2 treatment groups to 80% vs some 65% respectively. With regard to night pain very little difference was evident between the 2 groups (figure 43). In patients receiving famotidine the median number of days to relief of both day and night pain was proportional to the severity





of pain at the outset; this was not the case in patients receiving placebo (table 54). In patients receiving famotidine, the median number of days to relief of both day and night pain was 5 in patients starting with mild pain, 14 in patients starting with moderate pain and 28 in patients starting with severe pain.

TABLE 54
Time to Relief of Pain

		FAMOTIDINE (N=149)	PLACEBO (N=145)
Baseline =	Day Pain		
	None*	1.0 (n = 8)	21.5 (n = 6)
	Mild	5.0 (n = 31)	31.5 (n = 32)
	Moderate	14.0 (n = 68)	35.0 (n = 60)
	Severe	28.0 (n = 41)	35.0 (n = 47)
	All**	14.0 (n = 149)	35.0 (n = 145)
Baseline =	Night Pain		
	None	1.0 (n = 54)	1.0 (n = 45)
	Mild	5.5 (n = 22)	18.0 (n = 30)
	Moderate	14.0 (n = 43)	21.0 (n = 41)
	Severe	28.0 (n = 26)	28.0 (n = 29)
	All**	5.0 (n = 149)	14.0 (n = 145)

* Some patients had no pain at baseline but had pain at one or more subsequent timepoints
** Significant difference between treatment groups ($p < 0.01$)

(c) Antacid consumption: the percentage of patients taking antacids (figure 44) was quite high in both groups, but at all intervals was higher in patients on placebo than in those on famotidine. Since there are no data on the number of antacid doses taken, it is not known whether there is any clinical significance in these differences. The average number of days of antacid consumption (table 55) was statistically but not clinically significantly higher with placebo.

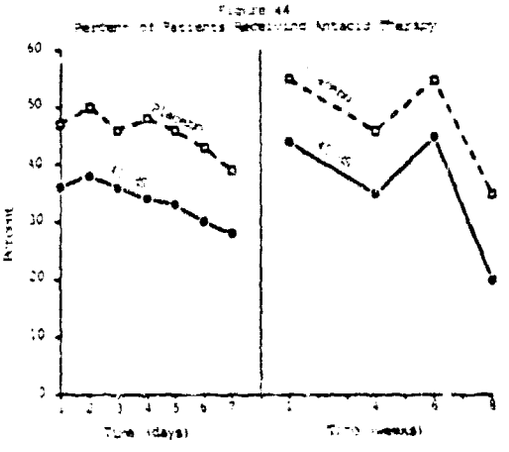


TABLE 55
Antacid Consumption
Mean Days of Antacid Therapy, Mean ± Standard Deviation

	Famotidine 40 mg HS			Placebo			Number of Days Difference Between 40 mg HS and Placebo
WEEK	N	MEAN		N	MEAN		
1	149	3.4	± 3.0*	145	3.2	± 3.2	+0.8
4	142	1.7	± 2.8*	137	2.7	± 3.2	-1.0
6	135	1.4	± 2.6*	129	2.1	± 3.0	-0.7
8	36	1.4	± 2.7*	48	2.2	± 3.2	-0.8

*Significantly different from the placebo group ($p < 0.05$).

(d) Patients global assessments (table 56): a remarkable observation is that good to excellent relief of symptoms at 4, 6 and 8 weeks respectively was reported by 64%, 70% and 74% of patients receiving placebo treatment. Nevertheless, an equal degree of symptomatic relief was reported in a sufficiently higher number of individuals receiving famotidine that the results with the drug were statistically significantly better than with placebo.

TABLE 56

Patients Global Assessments

TIMEPOINT	ASSESSMENT	FAMOTIDINE		PLACEBO	
		#	%	#	%
Week 4	Excellent/Good	108	80	85	64
	Fair/Poor/None	29	20	48	36
	Total*	137		133	
Week 6	Excellent/Good	125	86	99	71
	Fair/Poor/None	20	14	41	29
	Total*	145		140	
Week 8	Excellent/Good	127	88	102	73
	Fair/Poor/None	18	12	38	27
	Total*	145		140	
All Patients Treated	Excellent/Good	141	87	111	70
	Fair/Poor/None	21	13	47	30
	Total*	162		158	

*Significantly better ulcer healing for the famotidine group than for the placebo group ($p < 0.01$)

4. Study No. 746

a. Title of study: Comparison of famotidine vs Gefarnate in the short-term treatment of benign gastric ulcer.

[Gefarnate is a long-chain unsaturated fatty acid marketed in Japan, among other countries, for the treatment of gastric ulcer. In the sponsor's opinion it is tantamount to a placebo.]

b. Design of study: in this multi-center, double-blind, randomized, active control trial patients with endoscopic evidence of a single-gastric ulcer, circular or oval in shape, were assigned to receive either famotidine 20 mg b.i.d. or Gefarnate 100 mg t.i.d. Matching placebos were taken at appropriate times utilizing a double-dummy technique. Antacid was supplied for relief of ulcer pain as necessary. Each dose was equivalent to 0.6 gm of dried aluminum hydoxide gel and the frequency of dosing was limited to 10 times per week.

Exclusion criteria included ulcers of the pyloric channel and esophagogastric junction, a history of gastric surgery (including vagotomy), nursing, confirmed or suspected pregnancy, or severe concurrent disease.

Baseline evaluation consisted of history, physical examination, laboratory studies, gastric endoscopy and biopsy. Physical examination and laboratory studies were repeated at weeks 4 and 8.

Healing was defined as complete epithelization, regardless of associated gastritis or erosions.

c. Investigators (table 57): investigators at 32 Japanese centers participated.

Table 57

Country/Name	Affiliation	Location
Japan		
Yachi, Akira	Internist	Sapporo Medical College, Sapporo, Hokkaido
Ishimori, Akira	Gastroenterologist	Tohoku University, Sendai-shi, Miyagi Pref.
Seriguchi, Toshikazu	Internist	Gunma University, Maebashi-shi, Gunma Pref.
Sakita, Takeo	Internist	The University of Tsukuba, Tokyo Mitharai-gun, Ibaraki Pref.
Kitamura, Tetsuya*	Internist	University of Tokyo, Bunkyo-ku, Tokyo
Takeuchi, Tadashi	Gastroenterologist	Tokyo Women's Medical Coll., Shinjuku-ku, Tokyo
Omata, Shozo	Gastroenterologist	Yokohama Chiharo Hospital, Hodogaya-ku, Kanagawa Pref.
Honda, Toshio	Internist	Nihon University, Kanda Chiyoda-ku, Tokyo
Umeda, Moritsugu	Gastroenterologist	Matsuo Medical Center Hosp., Shinjuku-ku, Tokyo
Hondo, Hoshio	Internist	Icho Hospital, Shinjuku-ku, Tokyo
Kubota, Tuzuru	Internist	St. Luke's Int'l Hospital, Chuo-ku, Tokyo
Takasu, Sachio	Gastroenterologist	Kanto Teishin Hospital, Chinagawa-ku, Tokyo
Tsuchiya, Masanara	Gastroenterologist	Keio University, Shinjuku-ku, Tokyo
Sugata, Fumio	Gastroenterologist	Showa University, Yokohama, Kanagawa Pref.
Okabe, Haruya	Internist	Kitasato University, Sagamihara-shi, Kanagawa Pref.
Miwa, Takeshi	Internist	Tokai University, Isehara-shi, Kanagawa Pref.
Okabe, Kazuhiko	Gastroenterologist	St. Marianna University, Kawasaki-shi, Kanagawa Pref.
Watanabe, Yozo	Surgeon	Juntendo University, Bunkyo-ku, Tokyo
Kaneko, Eigo	Internist	Hamamatsu University, Hamamatsu-shi, Shizuoka Pref.
Nakazawa, Saburo	Internist	Nagoya University, Nagoya, Aichi Pref.
Takeuchi, Toshihiko	Internist	Nagoya City University, Nagoya, Aichi Pref.
Suyama, Tetsuji	Gastroenterologist	The Ctr. for Adult Diseases, Moriyama-shi, Shiga Pref.
Ohmino, Haruto	Internist	Kyoto University, Kyoto-shi, Kyoto
Kawai, Keiichi	Internist	Kyoto Prefectural University, Kyoto-shi, Kyoto
Yukawa, Eiyo	Gastroenterologist	Yukawa Icho Hospital, Tennoji-ku, Kyoto
Shimoyama, Takashi	Internist	Hyogo College of Medicine, Nishinomiya, Hyogo Pref.
Kita, Shoichi	Internist	Kawasaki Medical College, Okayama-shi, Okayama Pref.
Ohe, Keiji	Internist	Hiroshima University, Hiroshima-shi, Hiroshima Pref.
Mori, Hiroyoshi	Gastroenterologist	University of Tokushima, Tokushima-shi, Tokushima Pref.
Hisawa, Taoshi	Internist	Kyushu University, Fukuoka-shi, Fukuoka Pref.
Inoue, Mikio	Internist	Fukuoka University, Fukuoka-shi, Fukuoka Pref.
Yunoki, Kazuo	Internist	Kagoshima University, Kagoshima-shi, Kagoshima Pref.

d. Results

(1) Comparability of treatment groups (table 58): there were 96 patients in each group; the 2 groups were comparable in all essential respects.

(2) Exclusions from analysis of effectiveness (table 59): almost all of the 23% of patients lost to analysis were a result of failure to start therapy within 6 days of the baseline endoscopy; this left for analysis 72 patients in the famotidine group, 75 in the Gefarnate group.

(3) Safety

(a) Vital signs (table 60): neither drug had any effect on vital signs.

TABLE 58

Comparability of Treatment Groups at Baseline

	Famotidine 20 BID N = 96		Gefarnate 100 TID N = 89	
Age (years)				
Mean	47.5		47.1	
Median	48.0		48.0	
Sex				
Males	75	(78%)	71	(75%)
Females	21	(22%)	24	(25%)
Initial Ulcer Site (cm)*				
Mean	1.4		1.4	
Median	1.2		1.3	
Age at First Ulcer (years)				
Mean	46.3		44.3	
Median	47.0		45.0	
Duration of Ulcer Disease (years)				
Mean	7.5		6.2	
Median	3.0		3.0	
Ulcer History				
None	58	(60%)	55	(62%)
Single	15	(16%)	9	(10%)
Multiple	23	(24%)	25	(28%)
In/Out Patient Status				
In-Patient	5	(5%)	8	(9%)
Out-Patient	91	(95%)	80	(91%)
Prior Ulcer Therapy (within 7 days)	24	(25%)	23	(24%)

* Although only patients with single ulcers were allowed by protocol, some patients with multiple ulcers were entered. For patients with more than one ulcer, this was the size of the largest ulcer. For those patients, all ulcers must have healed to be considered healed.

TABLE 59

Exclusions from Analysis of Effectiveness

	Famotidine 20 BID	Gefarnate 100 TID
Off Drug	1	1
Concomitant Drug	1	1
Endoscopy missing or out of range	22	19
TOTAL	24 (25%)	21 (22%)

TABLE 60

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE FROM BASELINE
Body weight (kg)	Famotidine 20 BID	28	72.6	72.0	-0.4
	Gefarnate 100 TID	29	72.4	70.2	-2.2
Pulse (beats/min)	Famotidine 20 BID	23	55.6	56.2	+0.6
	Gefarnate 100 TID	24	55.0	55.6	+0.6
Systolic BP (mmHg)	Famotidine 20 BID	46	122.3	122.8	+0.5
	Gefarnate 100 TID	46	122.2	120.4	-1.8
Diastolic BP (mmHg)	Famotidine 20 BID	46	76.7	75.0	-0.7
	Gefarnate 100 TID	46	75.3	73.8	-1.5

(b) Clinical adverse experiences: drug-related adverse symptoms occurred in 5 patients receiving famotidine, 17 receiving Gefarnate (table 61). The most commonly reported adverse symptoms were constipation, occurring in 4 (4.2%) of the patients and nausea, occurring in 2 (2.1%) in each group. Two serious clinical adverse experiences occurred in each of the treatment groups, gastric cancer and a cerebral vascular accident in the famotidine group, gastric cancer and gastrointestinal bleeding in the Gefarnate group. Of these, only the case of hemorrhage was considered possibly drug-related. Two patients in addition to these, both receiving Gefarnate, were withdrawn because of adverse experiences (table 62), one because of diarrhea/nausea, the other because of weight loss, both considered possibly/probably drug-related.

TABLE 61

Drug-Related* Clinical Adverse Experience

ADVERSE EXPERIENCE	FAMOTIDINE	GEFARNATE
Body as a whole	0	0
Abdominal Pain	0	1
Digestive System	5	15
Anorexia	0	4
Constipation	3	3
Diarrhea	1	3
Eructation	0	2
Flatulence	1	2
Gastrointestinal Hemorrhage	0	1
Heartburn	0	2
Nausea	2	2
Vomiting	1	0
Peptic Ulcer	0	1
Metabolic/Nutritional System	0	1
Weight Loss	0	1

*"Possibly", probably" or "definitely" related to test drug in investigator's opinion. Total numbers represent counts of patients, not counts of adverse experiences.

TABLE 62

Patients Withdrawn Due to Adverse Experience

TREATMENT	AGE	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP POSS./PROB.
Famotidine (n=96)	183	Stomach Cancer	Severe	Definitely not
	424	CVA	Severe	Probably not[a]
Gefarnate (n=96)	102	Gastrointestinal bleeding	Severe	Possibly
	21[b]	Diarrhea/Nausea	Moderate	Possibly
	26[b]	Weight Loss	Severe	Probably
	292	Gastric Cancer	Severe	Definitely not

a (Probably not) Hemorrhage

b Also considered [illegible] relations

(c) Laboratory adverse events: 15 patients receiving famotidine and 14 receiving Gefarnate were found to have abnormal laboratory values; none resulted in withdrawal from the trial. Of the 2 events considered serious, a patient on famotidine developed thrombocytopenia (probably not drug-related) and one on Gefarnate had a drop in hemoglobin and red cell count (considered drug-related).

(4) Effectiveness

(a) Incidence of healing (table 63): at all 3 intervals evaluated (4 weeks, 8 weeks and later than 8 weeks) the incidence of healing with famotidine was statistically significantly superior to that with Gefarnate. The final incidence of healing with famotidine was 54/72 (75%), with Gefarnate 23/75 (31%). This is not an impressive record for famotidine considering that the incidence of healing at 8 weeks, 46/72 (64%), was much less than that (77%) in the European multi-center trial. However, judging from my experience with Japanese patients in Hawaii, gastric ulcer may be a different disease in Japanese than in occidentals.

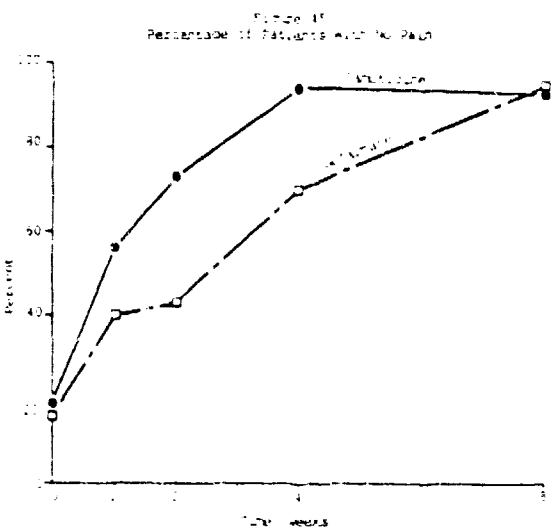
TABLE 63

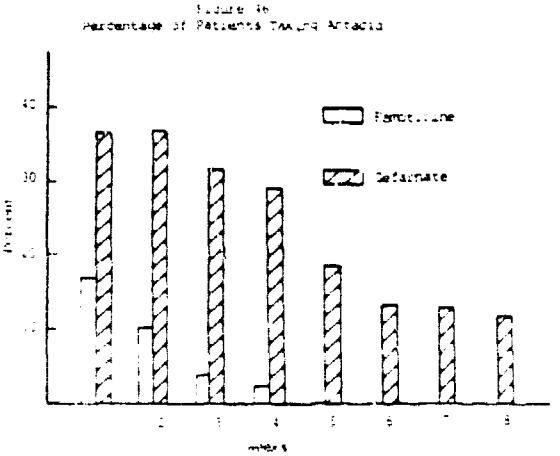
Cumulative number healed/number evaluable (%)

Week	Endoscopic range, days	Famotidine n=72	Gefarnate n=75	p
4	Up to 32	19 (26)	3 (4)	0.01
8	33 to 60	46 (64)	18 (24)	0.01
Later	61 to 124	54 (75)	23 (31)	0.01

(b) Relief of pain (figure 45): the percentage of patients relieved of pain was statistically significantly higher in patients receiving famotidine at the end of 1 week (2-8 days), 2 weeks (9-15 days) and 4 weeks (16-32 days). Thereafter the percentage of patients relieved of pain was approximately 90% with both treatments.

(c) Antacid consumption (figure 46): during the first 4 weeks the percentage of patients taking antacids was far less in patients receiving famotidine. After 4 weeks none of the patients receiving famotidine were taking antacids, while 10-20% of those receiving Gefarnate were continuing to do so.





(d) Investigators' global evaluations (table 64): the data show that the incidence of symptomatic relief greatly exceeds the incidence of healing, confirming what has long been an article of faith in the annals of peptic ulcer disease.

TABLE 64

Investigators Global Evaluation

Cumulative number markedly improved/number evaluable (%)

Marked improvement	Famotidine	Gefarnate	p
Week 4	55/76 (72)	17/80 (21)	0.01
Week 8	69/77 (84)	31/79 (39)	0.01

IV. Summary of NDA 19-462

A. Clinical pharmacology: famotidine was well-tolerated in volunteer subjects in doses at least twice the oral and intravenous recommended therapeutic doses. No serious adverse events, either in the form of symptoms or laboratory value deviations were encountered. Bioavailability was in the range of 40-45%. The half-life of the drug was of the order of 3 hours. Famotidine administered orally suppressed pentagastrin-stimulated gastric acid secretion in a dose-related fashion. The acid inhibiting effect of famotidine 5 mg was equivalent to that of cimetidine 300 mg. Twelve hours after administration of famotidine 20 mg, inhibition of pentagastrin-stimulated acid ranged from 16 to 88% with a mean of 54%. Doses of 20 or 40 mg b.i.d. suppressed nocturnal acid secretion more than

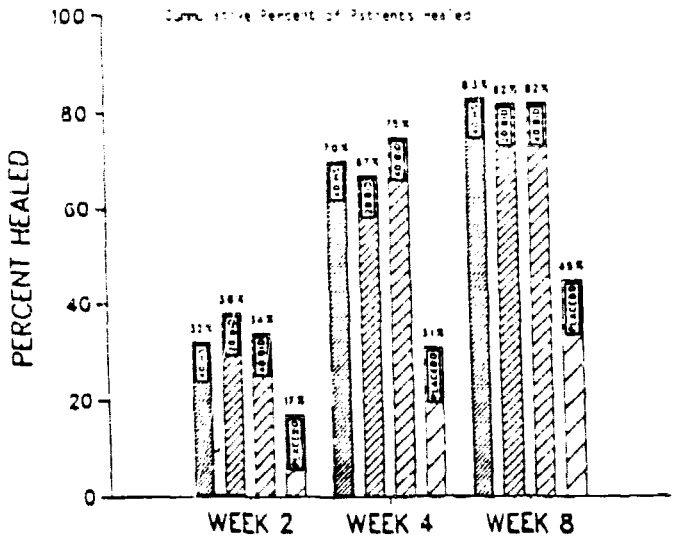
90% and meal-stimulated secretions an average of 41% and 57% respectively. A single-dose of 40 mg at bedtime inhibited nocturnal acid secretion, with a carryover effect on the acid response the next morning's breakfast meal. No cumulative effect was observed when famotidine was given over a period of 5 days. Doses of 20 or 40 mg given at bedtime inhibited breakfast, but not lunch- or dinner-stimulated acid secretion. An additional dose given following breakfast did reduce the acid response to the noon meal. The results of these tests of the effect of famotidine on acid secretion were the basis of the decision to include doses of 40 mg h.s., 20 mg b.i.d. and 40 mg b.i.d. in clinical trials of healing of duodenal ulcer.

Blood levels of prolactin, FSH, LH, and testosterone were not altered by administration of famotidine; there was a slight increase in serum gastrin. In a study designed to evaluate the effect of famotidine on hepatic metabolic function, famotidine did not induce changes in elimination of aminopyrine or antipyrine in most subjects. The significance of this observation was tested in drug-interaction studies, the results of which indicated that famotidine does not alter the pharmacokinetics of theophylline, warfarin, phenytoin or diazepam.

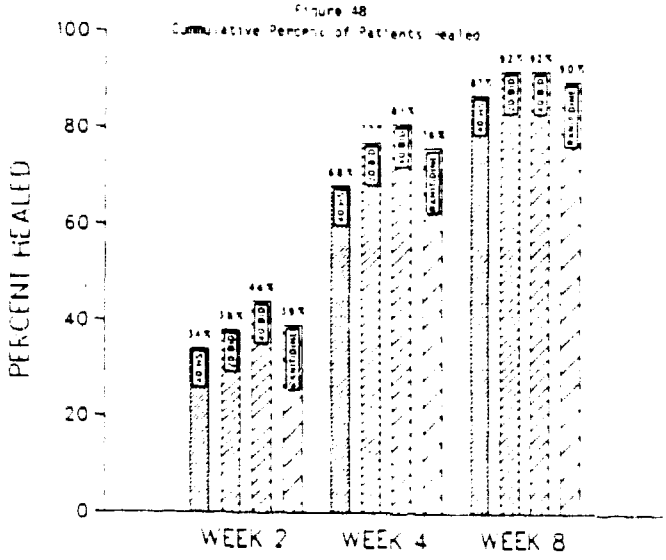
B. Effectiveness

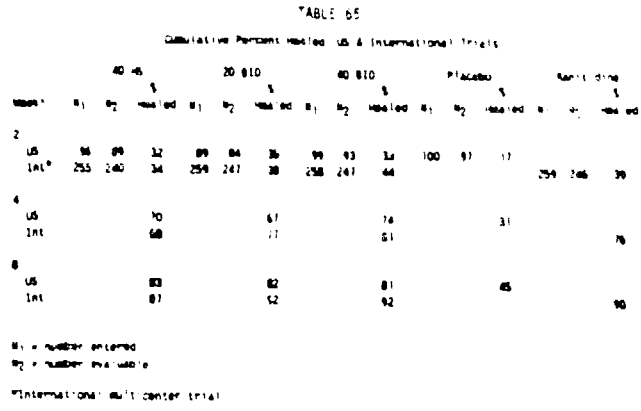
1. Short-term treatment of duodenal ulcer

a. Incidence of healing: 2 multi-center trials evaluated the incidence of healing with 3 dosage regimens of famotidine (40 mg h.s., 20 mg b.i.d., and 40 mg b.i.d.) one a United States trial comparing famotidine with placebo, the other an International trial comparing famotidine with ranitidine. In both trials the patients were endoscoped at 2, 4 and 8 weeks, the last endoscopy being at the first interval of healing, i.e. in the analysis of the cumulative incidence of healing, a patient whose ulcer was found to be healed at 2 weeks was considered to be healed at 8 weeks. The patients were given diary cards for recording episodes of pain and number of antacid doses taken. In the United States trial 34 investigators entered a total of 384 patients approximately equally distributed among the 4 treatment groups. All of the doses of famotidine were statistically significantly superior to placebo (figure 47); the incidence of healing with the recommended dose of 40 mg h.s. at 4 and 8 weeks was 70% and 83% vs 31% and 45% with placebo (p 0.01). In the International trial 68 investigators entered a total of 1,031 patients with approximately equal numbers in the 4 treatment groups. The



incidence of healing (figure 48) with famotidine 40 mg h.s. at 4 weeks (68%) was less than that with ranitidine 150 mg b.i.d. (76%) but at 8 weeks they were equal (87% vs 90%). Comparing the results of the U.S. and International trials (table 65) the incidence of healing was the same with the dose of 40 mg h.s., but with the b.i.d. doses the incidence of healing was higher in the International trial at both 4 and 8 weeks.





b. Relief of pain: ulcer pain was relieved sooner and in a higher percentage of patients receiving famotidine than in those receiving placebo. When compared with ranitidine, pain relief with famotidine was not significantly different.

c. Antacid consumption: in the U.S. study the number of days on which antacids were taken, the number of antacid tablets taken and the percentage of patients taking antacids all favored famotidine over placebo by statistical analysis, but the differences were not clinically meaningful.

2. Prevention of recurrence of duodenal ulcer: the role of famotidine in the prevention of recurrence of duodenal ulcer was evaluated in 2 multicenter, placebo-controlled trials in patients whose ulcers had healed during the short-term treatment were eligible for admission to a trial of famotidine vs placebo in the prevention of recurrence of ulcer. In the U.S. trial 26 investigators entered 177 patients, 54 on 40 mg h.s., 57 on 20 mg h.s. and 66 on placebo. The incidence of recurrence at all intervals up to 6 months (figure 49), which was the cutoff time for analysis of the data, was significantly lower with famotidine. At 6 months the incidence with 40 mg h.s. was 30%, with 20mg h.s. 26%, with placebo 70%. The incidence of recurrence with 20 mg h.s. was not statistically significantly different from that with 40 mg h.s. In the International trial, 64 investigators entered 471 patients, 237 on 20 mg h.s. and 234 on placebo. The incidence of recurrence (figure 50) on both placebo and famotidine was similar to that in the U.S. trial. Thus, in both trials, the recommended dose of famotidine for prevention of recurrence (20 mg h.s.) was statistically significantly superior to placebo (Table 66).

Figure 49
Cumulative Incidence of Relapse (%)

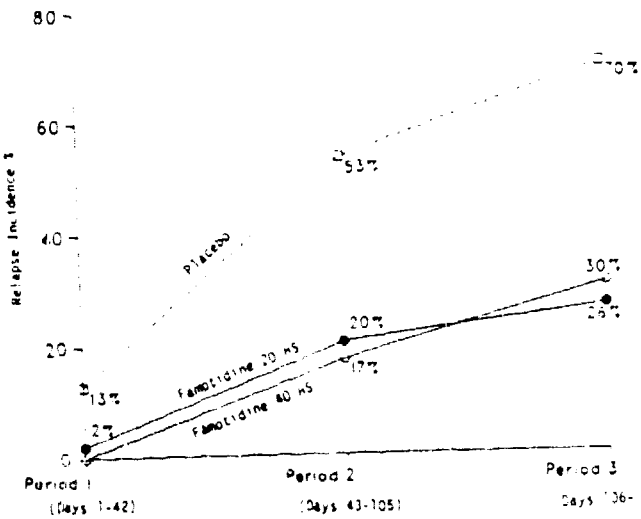


Figure 50
Cumulative Incidence of Relapse (%)

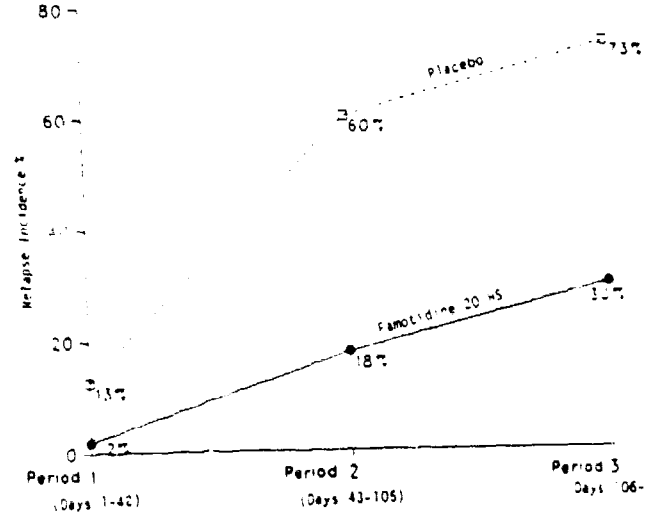


TABLE 66
Cumulative Life-Table Incidence of Recurrence (%)
U.S. and International Trials

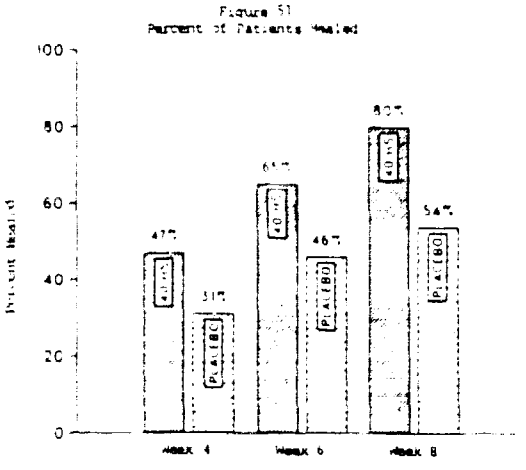
	40 mg		20 mg		Placebo		p
	n	% Recurred	n	% Recurred	n	% Recurred	
Days 1-42							
U.S.	54	0	57	1.8	66	12	
International			268	1.9	306	12.1	
Days 43-105							
U.S.	46	15.2	49	17.8	47	51.4	
International			237	17.6	234	60	
Days 106 or later							
U.S.	22	30.6	32	25.5	19	66.7	
International			162	29.8	95	73.1	

3. Treatment of gastric hypersecretory conditions: two studies were conducted in the United States on small series of patients with gastric acid secretion in the pathological range, all with suspected or proven Zollinger-Ellison syndrome. These patients had previously been treated with either cimetidine or ranitidine or both. The mean minimum daily doses expressed as grams/day required to suppress gastric acid secretion to less than 10 mEq/h during the 6 hours after administration of the drugs were famotidine 0.24, ranitidine 2.1 and cimetidine 7.8. Besides greater potency famotidine also had a longer duration of action than either of the other two H_2-blockers. Like ranitidine, but in contrast to cimetidine, famotidine was not associated with anti-androgenic side-effects. There is as yet no evidence that the higher potency and longer duration of action of famotidine will translate into dosage intervals less than 6 hours for adequate control of the gastric acid output.

4. Short-term treatment of gastric ulcer:

a. International multi-center trial: the only placebo controlled trial of famotidine in the short-term treatment of gastric ulcer was conducted in 14 countries with the participation of 44 investigators. A total of 336 patients were entered, 167 on famotidine 40 mg h.s., 169 on placebo.

(1) Incidence of healing: the proportion of patients whose ulcers healed was statistically significantly greater at all time intervals (4, 6 and 8 weeks) in patients receiving famotidine than in those receiving placebo (p 0.01)(figure 51). The incidence of healing with famotidine at the respective intervals was 47%, 65% and 80% in contrast to the respective percentages of 31, 46 and 54 with placebo.

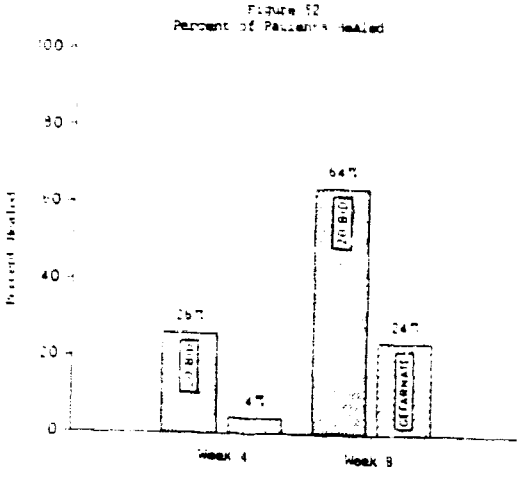


(2) Relief of pain: both day and night pain were more rapidly relieved in patients receiving famotidine.

(3) Antacid consumption: concomitant use of antacids was statistically significantly lower for patients treated with famotidine, but the difference was not enough to be of clinical importance.

(4) Patients' assessment of global response: at all time points patients in both groups claimed good to excellent symptomatic response in statistically significantly higher proportions than those who rated their responses as fair, poor or none, and in significantly higher proportions in patients receiving famotidine than in those receiving placebo.

2. Japanese clinical trial: the procedure was essentially the same as that in the International multi-center study except that the comparison was between famotidine 20 mg b.i.d. and Gefarnate 100 mg t.i.d. Investigators from 32 centers in Japan contributed a total 192 patients, 96 in each of the treatment groups. The incidence of healing of the gastric ulcers (figure 52) was much lower in the patients receiving famotidine than was the case in the International multi-center trial, possibly because the dosage of famotidine used in this trial (20 mg b.i.d.) is not comparable to that in the International trial (40 mg h.s.) and possibly because in the Japanese population gastric ulcer is a more resistant disease. The incidence of healing with famotidine vs Gefarnate was 26% vs 4% at 4 weeks and 64% vs 24% at 8 weeks.



The percentage of patients without pain was statistically significantly higher at all time points up to, but not including, 8 weeks in patients receiving famotidine. The percentage of patients taking antacids was significantly less with famotidine than with Gefarnate. Antacids were not required after the 4th week in patients on famotidine, but continued to be required in approximately 15% of patients taking Gefarnate up to 8 weeks.

V. Safety

Safety data updated to November 18, 1985 were available from 2,333 patients in world-wide trials. The most common clinical adverse experiences are headache (4.7%), diarrhea (1.7%), nausea (1.5%), constipation (1.3%) and dizziness (1.2%). The laboratory data indicate no evidence of serious drug-related hematological, hepatic or renal toxicity. The safety profile of famotidine will only become apparent, however, in the market place.

There were 19 deaths in the world-wide experience, none of them drug-related (table 67), only 3 of which occurred in patients treated for indications addressed in this NDA.

TABLE 67

Deaths in Patients Treated with famotidine

Ident.	Age	Sex	Immediate Cause	Concurrent Condition	Route of Administration	Indication
				JAPAN		
Japan	24	M	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
Japan	41	M	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
Japan	44	F	Hepatic failure	GI hemorrhage/ fulminant hepitits	I.V.	stress ulcer
Japan	55	M	Hepatic failure	GI hemorrhage fulminant hepatitis	I.V.	stress ulcer
Japan	68	M	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
2103	Unk*	Unk	Unknown	GI bleeding/stress ulcer, Colon cancer	I.V.	stress ulcer
2104	Unk	Unk	MI**; Renal failure	GI hemorrhage/stress ulcer, MI (past)	I.V.	stress ulcer
2105	Unk	Unk	Respiratory failure	GI hemorrhage/stress ulcer, Colon cancer Renal insufficiency	I.V.	stress ulcer
0704	Unk	Unk	Unknown	GI hemorrhage/stress ulcer, Perforation of stomach, Rheumatoid arthritis	I.V.	stress ulcer
2501	72	M	Hepatic failure	GI hemorrhage/stress ulcer, Hepatoma, Subphrenic abscess	I.V.	stress ulcer
2702	58	M	Hepatic failure	GI hemorrhage/stress ulcer, Pancreatitis, Liver cancer, Cirrhosis; Cholelithiasis	I.V.	stress ulcer
3602	62	M	Unknown	GI hemorrhage/stress ulcer, Bladder cancer	I.V.	stress ulcer
				INTERNATIONAL		
1895	71	M	Myocardial Infarction	—	oral	maintenance therapy
718	44	M	Peritonitis	Cirrhosis of liver	I.V.	stress ulcer
20005	86	F	Respiratory failure	Pneumonia	oral	peptic ulcer
709	46	F	Septicemia	Third degree burns on 60% of body, pneumonia	I.V.	stress ulcer
718	23	M	Brain infarctions	—	I.V.	stress ulcer
700	75	F	Abdominal infection	Volvulus of small bowel with necrosis	I.V.	stress ulcer
				U. S.		
3	64	F	"Natural"	—	oral	Zollinger-Ellison Syndrome

*Unk = Unknown
**MI = Myocardial infarction

VI. Package insert: the insert (attached) is generally factually correct but is unnecessarily repetitive. I have indicated my suggestions for revision.

VII Conclusions

A. Pepcid (famotidine) is safe and effective in the following dosage for the following indications:

1. 40 mg h.s. for the short-term (4-8 weeks) treatment of duodenal ulcer.

2. 40 mg h.s. for the short-term (4-8 weeks) treatment of gastric ulcer.

3. 20 mg q 6h initially and increased as necessary to reduce gastric acid output below 10 mEq/hr in the treatment of Zollinger-Ellison syndrome.

B. Data from 2 6-month trials of prevention of recurrence of duodenal ulcer show that famotidine is more effective than placebo but do not provide a sufficiently long follow-up (at least one year) to permit a final assessment of the effectiveness of famotidine for this indication.

VIII Recommendations: Approve the application for the following indications and dosages:

1. 40 mg h.s. in the short-term (4-8 weeks) treatment of duodenal ulcer.

2. 40 mg h.s. in the short-term (4-8 weeks) treatment of gastric ulcer.

3. 20 mg q 6 h, increased as necessary to keep gastric acid output below 10 mEq/hr in the treatment of Zollinger-Ellison syndrome.

William H. Bachrach

William H. Bachrach, M.D.

cc: Orig. NDA 19-462
HFN-110
~~HFN-110/CSO~~
HFN-110/WHBachrach
rq:12-21-85:12-26:12-30:0409r

PHARM REV

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

NDA 19-462 Pepcid (famotidine) August 26, 1985
Merck Sharpe & Dohme

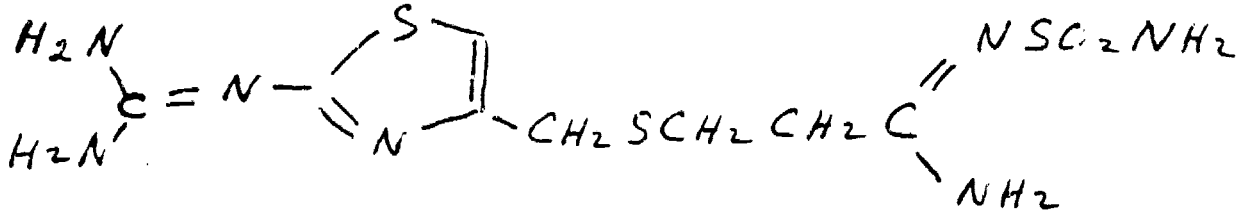
ORIGINAL SUBMISSION CD&B RECEIPT DATE: 6/24/85

Pharmacology Review
(Original Summary)

1. Name of Drug: Pepcid (famotidine) or MK-208

2. Category: Histamine H2 receptor antagonist

3. Chemical Structure:



Famotidine

4. Composition and Dosage Form:

	mg/per tablet
Famotidine.....	20 or 40
plus inactive ingredients	

5. Indications: Short-term treatment of active duodenal and gastric ulcers, long-term prevention of duodenal ulcer recurrence, and long-term management of pathological hypersecretory conditions such as Z-E Syndrome.

6. Dosage: Recommended adult dose is 40mg at bedtime for acute duodenal or gastric ulcer. The maintenance dose to prevent ulcer recurrence is 20mg at bedtime. For Z-E the dose is usually 20mg q.i.d. but could range up to 160mg q.i.d. In patients with renal insufficiency, dosing may be every other day for whatever indication.

7. IND UNDER WHICH CLINICAL STUDIES CONDUCTED: [redacted] MSD.

8. Submitted Preclinical Data: These studies were largely conducted either by Yamanouchi Pharm. of Japan (Y) or Merck Sharpe & Dohme (MSD). Many of these studies were reviewed in the past in conjunction with [redacted] The following summarizes preclinical data that have not been previously reviewed. For the sake of brevity, the letters F, C, and R are used for Famotidine, Cimetidine, and Ranitidine respectively.

A) Acute Toxicity:

Dogs:

Four dogs treated at separate times with single oral doses ranging from 10 to 2000mg/kg showed no adverse effects (clinical, ECG, serum biochem, body weight, hematology, urinalysis). When the same dogs were subsequently tested for 15 consecutive days with 1000mg/kg/day, they exhibited only slight weight loss and necropsy was normal.

Another set of dogs were tested acutely i.v. with a 2 or 3% formulation containing saline and L-Aspartic acid at doses ranging from 10 to 300 mg/kg injected at the rate of 10 ml/minute. No deaths occurred up to 200 mg/kg but one died at 300 mg/kg of unknown cause. The dose of 10 mg/kg i.v. caused no clinical reactions, but 30 & 100 mg/kg elicited emesis in 1/4 & 4/4 respectively. Clinical reactions at 200 mg/kg & higher were emesis, weakness, defecation, lacrimation, and sometimes conjunctival injection, inactivity, & prone posture at 300 mg/kg. Slight tachycardia occurred at 300 mg/kg, glucosuria & proteinuria at 100, 200, and 300 mg/kg, prominent GOT & GPT at 200 and 300 mg/kg, & hypokalemia at 300 mg/kg. Gross & microscopic exam were reportedly normal.

Rats: The injectable formulation of F when tested for acute i.v. toxicity in mice after exposure to conditions of degradation (2 months at 60°C) displayed an LD50 (410 mg/kg) which was comparable to undegraded material (306-438 mg/kg).

Six analogues of F which are either byproducts of synthesis or products of degradation were tested for acute toxicity. All showed either low toxicity or toxicity comparable to F except for one (A-4) It showed an LD50 of only 113 mg/kg and 225 mg/kg orally in mice and rats and an LD50 i.v. of 22 mg/kg and 18 mg/kg in same. However when a mixture of F and all of the 6 analogues, each analogue at a conc 5 times the expected, the oral LD50 of this mixture in mice was the same as normally manufactured material, i.e. 8000 mg/kg. A-4, which is a byproduct in the synthesis of MK-208, was nephrotoxic in rats treated acutely p.o.

B. Subacute Toxicity:

Rats In an i.v. study conducted by Huntingdon Research Groups of 15M and 15F rats were injected daily with 0, 4, 20, 100, or 200 mg/kg of F for 13 weeks.

Results

Clinical reactions following injection were observed in rats injected with 100 & 200 mg/kg. These included tremors, labored breathing, unsteady gait, pallor, and salivation. Survival was reduced at the top dose (4M & 5F deaths). Growth depression & increased water consumption was seen at the upper two levels, as well as anemia and slight increases in urea nitrogen and creatinine (the latter at 200). At necropsy, severe reactions were seen at the injection sites of 200 mg/kg treated animals and renal cortical scarring was seen in 5/15 and 10/11 male rats al 100 & 200 mg/kg. Stomach weights were increased at the upper two levels & adrenal weights in males treated with 200 mg/kg. Microscopic studies confirmed the gross finding in the injection sites at the top dose & the renal effects (foci of basophilic tubules or tubules with flattened epithelium in 3/15, 3/10, 3/10, 7/10, and 11/11 male rats of the C, L, M, + H levels). The concentration of drug used at the top dose was 3.3% (.07 to 1.7% at the lower levels which did not show undue irritation histologically). The stomachs were said to be normal histologically.

Dogs: In a range-finding study conducted by Y beagles were injected i.v. with 0, 100 and 200 mg/kg/day of F for 2 wks. The injection rate was 10 or 20 ml/minute and the conc. of the drug was 2%.

Results: No deaths occurred but distnict clinical reactions were elicited in a dose related way. The reactions were emesis, salivation, conjunctival injection (top dose), collapse (top dose after injection) & associated defecation. No other effect (including biochemical, gross & histological) were seen.

C. Chronic Studies:

Rats

1) In a study conducted by MSD to evaluate the reversibility of eosinophilic cytoplasmic granularity (ECG) of gastric chief cells, groups of 60 male S-D rats were gavaged with 0 or 2000 mg/kg/day of F for 182 days. Twenty rats per group were sacrificed at term (182 days) and the remainder after a 14 wk recovery period.

Results

After 182 days slight ECG of chief cells was seen in 5/24 (21%) controls and 14/20 (70%) treated. After the 14 wk recovery period the incidence was 11/36 (31%) controls and 11/40 (28%) treated, thus indicating reversibility of the effect.

2) A second reversibility study was conducted by Y in two groups of 60 M CRCD rats at oral doses of 0 and 200 mg/kg. Treatment lasted 24 wks & the post-treatment recovery period was 18 wks. Another reversibility study conducted by Y in SD rats entailed the oral administration by gavage of 0 or 2000 mg/kg of F to two groups of 70 to 107 rats for up to 43 wks. Interim autopsies were made at weeks 13, 26, 37 & 39 and at 5 & 13 wks post drug (recovery phase). Subgroups included controls and test animals receiving acid drinking water for 43 wks, at which time they were sacrificed. A fourth reversibility study was done (see below).

Results

In the first study gastric chief cell eosinophilic granularity (ECG) was observed in 10/16 and 11/17 animals treated with 200 mg/kg of F for 14 & 22 wks vs 0/15 & 1/17 controls at corresponding times. Sixteen weeks after discontinuation of treatment in week 24, the incidence of ECG was 1/27 & 1/28 in the treated & controls respectively.

In the second study, the number of incidence ECG cells as cell as the intensity of ECG cell proliferation increased in the drug treated animals as early as 13 wks; these effects intensified over the course of treatment. HCl acid in the drinking water did not prevent or enhance the ECG cell proliferation in the drug treated. There was partial regression of the enhanced number of ECG cells in the test animals 13 wks after cessation of treatment.

In the third study, the ECG cell hyperplasia noted in rats tested for 43 wks was totally reversed 26 wks subsequently.

Dogs:

1) In a 26 week i.v. study conducted by Y groups of 4M & 4F beagles were injected daily with 0, 4, 25, or 100 mg/kg/day. The formulation used was a lyophilized preparation containing L-aspartic acid and dissolved in saline at a conc. of 2%.

Results

One dog at 100 mg/kg collapsed 2 minutes after the first injection & displayed reduced motor activity, decreased respiratory rate, pale mucus membranes & weak pulse. It recovered 3.5 hrs. after injection.

Dose related emesis occurred minutes after injection. Salivation occurred at the top dose as well as reddening of mouth and ears, possibly due to vasodilation , occasionally in 3/8 dogs.

The pulse rate of nearly all high dose dogs was prominently increased 1-3 minutes after injection during the entire study, but were unchanged at the lower doses (5 & 25mg/kg).

No adverse effects were seen in any of the other parameters (water intake, opthalmologic, serum biochem, hematology, myelographic, urinalysis). Injection sites were not unduly affected.

2) In a study identical to the previous one, groups of beagles were injected with 0, 5, 25, or 100 mg/kg for 26 wks; this study was conducted by Shin Nippon Labs.

Results

The results of this study were essentially identical to the previous one. The only notable differences was the presence of mucosal reddening (vasodilation) & slight tachycardia at the 25 mg/kg level as well as at the top dose and the absence of collapse of any treated dog.

D. Reproduction Studies:

1. Fertility & General Reproductive Performance: In a study (#81106) conducted by Y groups of 24M & 48F Sprague-Dawley rats were gavaged daily with 0,500, 1000, 12000 mg/kg for 12 weeks prior to mating & through mating in the case of the males & for 2 wks before mating, through mating & up to day 13 of gestation for 1/4 of the females, or up to day 20 for 1/2 of the females, or through natural delivery & up to weaning for 1/4 of the females. The development & reproductive capacity of the F1 generation was determined & the early growth of the F2 generation. Teratogenicity was determined by examination of the offspring delivered surgically at day 20 of gestation for gross, visceral, and skeletal defects.

Results

None of the test doses produced drastic impairment. Treated responded essentially like controls with respect to mating performance, fertility, fecundity, growth, development & fertility of the F1 generation, and status of the F2 generation. Nor was there any indication of teratogenicity, although the drug appeared to cause minor skeletal variations (increased ribs, sternebrae, and caudal vertebrae). The only offspring that was grossly deformed was a low dose pup with a vestigial tail.

Effects possibly due to F were increased neonatal deaths at the top dose & depressed growth of nurslings at upper two levels.

2) Fertility study #2. In an i.v. fertility study conducted by IRDC, groups of 25 M & 25 F Charles River rats were injected once daily for 60 days before & through mating for the males & for 14 days before mating & up to day 7 of gestation for females with 0, 30, 100, and 200 mg/kg. Offspring were delivered surgically on day 20 & examined for gross, visceral, & skeletal defects.

Results

Male & female fertility as well as in utero development of offspring were unaffected at all test levels. There was no indication of teratogenicity.

The only signs of toxicity were 5 male deaths at the mid dose and 8 males and 1 female at the top dose, all temporally associated with injection. Males seemed to be more sensitive to the drug. Finally, post-dose tachycardia was present in high dose males. Growth of males & females was reduced slightly at the higher levels.

3) Teratology Studies in Rats:

a) In a preliminary dose-range study (#80103) conducted by Y, groups of 12 pregnant C-R rats were dosed orally by catheter with 0, 500, 1000, or 2000 mg/kg of F during days 7-17 of gestation. One half of the animals were delivered surgically on day 20 and the remainder were allowed to deliver naturally.

Results

In this dose range-finding study, F was essentially without effect. The only questionable findings were in the group that delivered naturally & included slight increase in length of gestation at the low & high doses, slight reduction in live birth rate and delivery rate at the top dose. Since the number of animals used per group was small, and since the results in the caesarian group were normal, the few disturbances seen in the group that delivered naturally may not be drug related.

b) In an i.v. Teratology Study conducted by Yamanouchi groups of 30-37 pregnant C-R rats were injected i.v. with a 2% sol. of F at doses of 0, 30, 100, and 200 mg/kg during days 7-17 of gestation. Two thirds of the dams were delivered surgically on day 20 and the remainder were allowed to deliver naturally. The F1 offspring were examined for gross, visceral, and skeletal defects & those delivered naturally were allowed to reproduce.

Results

F caused clinical reactions at 10 and 200 mg/kg (ataxia, piloerection, reduction in motor activity, bradypnea, prostration) associated with injection. Three of 37 dams died at the top dose. Reproductive parameters were essentially undisturbed by all test doses of F. The only suggestions of reproductive impairment were slightly impaired growth of the male & female F1 offspring at the top dose, and slight reduction in the fertility of the F1 high dose animals. There was no evidence of teratogenicity (rate of terata low & comparable in all groups).

4) Teratology Studies in Rabbits:

a) Dose range-finding study by Yamanouchi in non-pregnant rabbits: Groups of five N.Z. White rabbits were gavaged once daily with 0, 500, or 2000 mg/kg of F for 14 days.

Results:

All rabbits survived but both dosages produced distinct toxicity, e.g. growth depression at the low dose & weight loss at the top dose, corresponding reductions in food consumption and dose related reductions in the absolute and relative weight of the liver. There were no clinical reactions & necropsy resealed no gross abnormalities of the thoracic and abdominal organs.

b) Dose range-finding study in pregnant Rabbits:

In the first study (#80106), groups of 8 pregnant N.Z. white rabbits were intubated once per day with 0, 200, 500, 1000, or 2000 mg/kg of F during days 6 to 18 of gestation.

In a second study (# 80111), groups of 5-8 pregnant N.Z. White rabbits were intubated with 0, 50, 100, or 200 mg/kg of MK-208 during days 6-18 of gestation. In both studies, animals were sacrificed on day 29.

Results

In the first study, F exerted toxic effects at all levels. This included abortions in 2/7 at 200 mg/kg, 4/6 at 1000 mg/kg, and 3/6 at the top dose. These abortions occurred six to eleven days after cessation of treatment on day 18 of gestation. Growth was depressed in a dose related way at all levels; growth was depressed during time of drug administration (days 6-18 of gestation), but continued to deteriorate after cessation of drug administration (days 18-29 of gestation). The dams experienced a mean weight loss at all dose levels.

Food consumption was depressed at all drug levels in a dose related way, more so after the period of drug administration. Necropsy revealed yellowish-brown livers in 3 dams at 200 mg/kg and 1 case each at the other drug levels.

There was a dose related reduction in the weight of the fetuses and of the placentae. There was also an increase in dead fetuses in the test groups. Gross anomalies were present in 1 each at the 2000 mg/kg and 1000 mg/kg (in each case included flexion of the left fore-limb) and in 6 from one litter at 500 mg/kg level (2 general edema & 4 edema of head region). Skeletal variants were absent but visceral anomalies included 2 cases of gall bladder defect at 200 mg/kg & one at 1000 mg/kg and one case of bifurcation of the cardiac apex at 2000 mg/kg.

In the second study, growth and food consumption were essentially unaffected up to 100 mg/kg; at 200 mg/kg, growth was depressed slightly.

No drug related deaths or abortions occurred. Whereas none of the 58 control fetuses showed anomalies, three of 46 high dose pups showed anomolies exencephaly, cleft palate, open eyelids & cataract in one, agenesis of the gall bladder with or without rib bifurcation in 2 others).

c) Rabbit Teratology Study (# 81101) by Yamanouchi)

Groups of 9-14 pregnant N.Z. white rabbits were intubated daily during day 6-18 of gestation with 0, 30, 200, or 300 mg/kg and sacrificed on day 29. Offspring were examined for external, visceral, and skeletal defects.

Results

The doses of 30 and 200 mg/kg were essentially without adverse effect. The only disturbances possibly related to drug administration were a transient mild depression of body growth at the beginning of drug treatment at 30 & 200 mg/kg, a slight increase in percent stillbirths at same (12 and 9% at L & M vs 7% in controls), and a reduction in the percent of lumbar ribs (28% vs 43% in controls). One mid dose mother aborted following severe anorexia & weight loss but this dam also showed evidence of accidental intubation at necropsy. The top dose was clearly toxic, causing severe anorexia & growth depression, 4 abortions (3 of which followed severe anorexia & weight loss), a distinct increase in stillbirths (16% vs 7% in controls) with a corresponding slight reduction in a g. live litter size, yellowish liver (fatty metamorphosis) most likely secondary to starvation in five dams. There were no external anomalies at any dose, but 2/77 pups at the high dose showed bent ribs and there was a decrease in the number of lumbar ribs in offspring from the upper two levels as well as a decrease in number of sacrocaudal vertebrae at the high dose. The latter variations reflect delayed ossification and are likely secondary to poor nutrition. The anorexia & weight loss which appeared during treatment with 500 mg/kg of F persisted and in some cases intensified after cessation of drug treatment on day 18 of gestation. All of the four abortions at the top dose occurred after discontinuation of drug treatment and in 3/4 cases was related with severe growth depression.

d) Intravenous dose range-finding studies in rabbits:

In three non pregnant rabbits, an acute I.V. dose of 100 mg/kg was non-lethal, but 200 mg/kg killed 1/3 and 400 mg/kg killed 2/2.

A study conducted by Yamanouchi utilized 2 groups of 3 pregnant N.Z. White rabbits injected I.V. with 50 or 200 mg/kg of F during days 6-18 of gestation. Reproduction was not drastically impaired, but one dam injected with 50 mg/kg aborted on day 27 and one pup from the top dose showed fusion of the 2nd and 3rd vertebrae. Clinical reactions, e.g. decreased activity & decreased muscle tonus occurred at the top dose only.

e) Intravenous Teratology Study in Rabbits (Study #81107 by Yamanouchi).

Groups of 13-14 pregnant N.Z. White rabbits were injected I.V. during days 6-18 of gestation with 0, 10, 30, or 100 mg/kg of F. After sacrifice on day 29, offspring were examined for external, visceral, and skeletal defects.

Results

None of the test doses produced significant disturbances of reproduction. But growth was somewhat depressed (no weight gain) at the low & mid doses and the percent of empty implantation sites was increased at the same doses. Two abortions occurred at the low dose to dams that showed only mild growth depression. The absence of a dose related relationship raises some doubt whether the aforementioned effects were causally related to the drug.

There was no clear evidence of teratogenicity; isolated anomalies observed in offspring of the test groups were retroesophageal right subclavian artery in one low dose pup, fusion of the 1st & 2nd thoracic vertebra & fusion of the 1st & 2nd rib in one low dose pup, fusion of 7th cervical vertebra and 1st thoracic vertebra with associated vertebrae body defects in a third low dose pup, and finally abnormalities of the thoracic vertebra & ribs in a high dose pup. These effects were not seen in controls.

f) Effect of oral and I.V. administration of F on food consumption in pregnant rabbits: In this study conducted by Yamanouchi, eleven N.Z. White rabbits were gavaged once daily with 500 mg/kg of F during day 6-18 of gestation and allowed to deliver naturally. After a suitable recovery period, the surviving dams were mated again and the six found pregnant were injected I.V. with 100 mg/kg during days 6-18 of gestation.

Results

In the oral phase, F quickly produced a state of total & persistent anorexia in 5/11 dams with an accompanying significant loss in body weight. Appetite & growth was not affected in the other animals. Between days 20 and 27 of gestation (after drug administration had terminated and while animals were still anorexic) the five dams showing appetite & growth suppression aborted. None of the other dams aborted.

In the I.V. study, no growth or appetite suppression was induced & no abortions occurred. The only fetus malformed was one showing exencephaly from a mother injected with 100 mg/kg I.V.

g) Plasma levels in pregnant rabbits

These groups of 5 pregnant N.Z. White rabbits were treated orally with 30, 200, and 500 mg/kg of F during days 6-18 of gestation. Plasma levels were determined at 2 hrs post drug on days 5, 12, & 18 of gestation and at hrs 6 & 24 on day 18.

Results

F produced a predictable depression of appetite & growth. Plasma levels were increased in a dose related manner at 2 hrs post drug at all times tested. However, they were substantially elevated at 24 hrs post drug only at the 500 mg/kg level, which is the threshold level for inducing abortions orally.

5. Peri - and Post - Natal Studies

a) Groups of 25 female rats were dosed orally from day 15 of gestation to the 21st day of weaning with 0, 100, 500, and 2,000 mg/kg of F. Growth, development, & fertility of the F_1 generation was assessed as well as effects on the F_2 generation.

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4) Reversion Test of purified & crude preparations of C-nitroso-F: Neither the purified nor crude nitrosamine forms of F were mutagenic, with or without metabolic activation, against various strains in the Ames test.

5) Repair Test:

F and cimetidine did not inhibit growth of B. subtili strains M45 and H_{17} up to 10 mg/plate, but tiotidine did slightly at the higher concentrations.

6) Repair Test of F, Cimetidine, & Tiotidine after reaction with nitrite:

After reaction with nitrite, both F & Tiotidine were highly positive (growth suppressing) against B - subtilis strains 5 and H_{17}. Each drug suppressed growth of the recombination repair deficient strain M45 much more than the wild strain H_{17}

7) Repair Test of pure & crude C-nitoso - F

Both forms suppressed M45 & H_{17} at the high concentration of 7320 microgram/plate but supression of M45 was not sufficient to reflect a mutagenic activity.

8) Micronucleus Test in Mice

Mice were treated orally for two days with 0.5, 1, and 2 g/kg, then sacrificed for examination of bone marrow cells. F did not cause chromosomal aberrations judged from the no. of polychromatic RBC's with micronuclei.

9) Mammalian Cell Mutagenesis Assay in chinese hamster lung fibroblasts:

In two separate tests, with or without metabolic activation, F did not induce mutation of Chinese hamster lung fibroblasts in vitro up to a conc. of 10 mM per plate whereas positive controls were active.

10) Mammalian Cell Mutagenesis Assay in Ovary cells:

In two separate assays, with or without metabolic activation, F did not induce mutation of Chinese Hamster ovary cells in vitro up to 3mM/plate whereas positive controls were active.

11) Chromosome Aberration Test in Mice.

Groups of 5 mice were treated orally with acute or [illegible]te (5 days) doses of 50, 100, or 200 mg/kg of F I.V. Twenty - hrs. after the last dose, bone marrow cells were examined for chromosomal abberations. The cells from mice treated acutely or subacutely did not show evidence of significantly increased chromosomal aberrations up to the maximum dose.

F) Special Studies

1) Effect on thyroid:

F administered for 5 wks to groups of 15 male rats at 0, 400, 1000, and 2000 mg/kg, did not affect serum level of thyroid hormones, nor the weight or histology of the thyroid gland.

2) Immunogenicity in mice:

F either alone or complexed to a carrier protein, was injected i.p. into mice. Following injection, no IgE antibody appeared up to 25 days after injection, however the positive control, DNF complexed to protein, produced obvious IgE titers.

3) Immunogenicity in G pigs

Groups of 8 g - pigs were injected s.c. three times at six day intervals with 1 or 10 mg/kg of F. Fourteen days after the last injection, the animals were challenged I.V. with F. No F treated died or showed anaphylactic reactions whereas 3/8 positive controls died.

4) Rabbit Eye Irritation:

Instillation of solutions of F up to 1% and at pH 5.5 caused no irritation to the eye or conjunctiva of rabbits.

5) Rabbit Muscle Irritation:

0.1 ml of 0.001% solution of F in distilled water caused no more irritation than saline & was much less irritating than the same volume of 0.75% acetic acid when injected one time into the vastus lateralis muscle of rabbits.

6) In vitro Hemolysis Test:

The injectable formulation (20 mg of F, 8 mg of L-aspastic acid, 40 mg of D-mannitol dissolved in 2 ml of distilled H_2O) caused no hemolysis in vitro in human or rabbit blood. Likewise, no hemolysis or precipitation resulted when two samples of same were tested on washed human RBCs.

7) Irritation in Dogs:

When the above injectable formulation was administered i.m., I.V., intraarterially, or perivenously to dogs at a dose of 2 ml (containing 20mg of F)one time at separate sites, no undue irritation was observed macroscopically or histologically at 24, 48, or 46 hrs. post-drug. Irritation at each test site was comparable to corresponding saline controls.

8) Infusion Study in dogs:

Groups of 3-4M & 3-4 F beagles were infused I.V. 6 hrs per day for 7 days with a 0.4% injectable formulation of F at doses of 0, 4, 12, & 36 ml/kg/day (equivalent to 0, 16, 48, and 144 mg/kg/day).

Results:

No dogs died & injection sites were not affected. The only indication of toxicity was emesis, hypoglycemia, and slight hypotension at the high dose only.

9) Skin Sensitization in G. Pigs:

Topical application of the injectable formulation of F did not elicit a sensitization reaction in the skin of G Pigs which had been previously treated intradermally & topically with the drug. This model reacted very positively to penicillin.

6) Pharmacology

1) In vitro histamine H_2 receptor antagonism:

In vitro, F inhibited histamine induced tachycardia of the isolated rt. heart of G. Pigs as well as histamine induced relaxation of the isolated rat uterus, showing 10 & 166 times the activity of C respectively. F also inhibited dimaprit induced tachycardia of the isolated G. Pig heart in a non-competitive unsurmountable way (unlike C & R which showed competitive surmountable antagonism). In the latter, F was bound rather tightly to the H_2 receptor in contrast to R and C which are removed easily through washing.

F inhibited histamine sensitive adenylate cyclase (and thus cyclic AMP formation) in membrane fragments of g. pig gastric mucosa and hippocampal homogenates of g. pig brain. It displayed a dose related competitive antagonism qualitatively similar but 24 times greater than that shown by C.

Like R, F inhibited in a competitive way the utilization of aminopyrine in isolated gastric glands of rabbits. This response reflected inhibition of gastric secretion.

Finally, F competitively and reversibly inhibited dimaprit induced relaxation of isoproterenol stimulated contraction of isolated g. pig lung strips.

F showed in vitro a lack of effect on responses mediated by H_1 - histamine, beta-adrenergic and muscarinic receptors, or acetylcholine release. It was also inactive in radioligand binding tests relating to dopaminergic, neuroleptic, serotoninergic, adrenergic, cholinergic and purinergic sites.

2. In vivo Antisecretory Activity:

F inhibited gastric secretion in gastric fistula dogs stimulated with either histamine, gastrin, 2-deoxy-D-glucose as well as food and dimaprit in Heidenhain pouch dogs. Activity was seen by both the I.V. and oral routes. The effect was characterized by a reduction in volume and in acid & pepsin output and to a lesser extent in acid concentration of gastric secretions. Comparative evaluations invariably showed F to be most potent by far, R intermediate, and C the least potent; against histamine stimulation in orally treated dogs, the most sensitive species tested, F was 95 times more active than C & 14 times more active than R on a weight basis & 127 & 15 times as active respectively on a molar basis. The oral and I.V. ED50 of F against histamine evoked gastric secretion in dogs was only 0.03 mg/kg in each case as compared to 2.86 mg/kg & 1.84 mg/kg respectively for C.

The time course of gastric antisecretory effect of F appeared to be somewhat longer than C or R. For example, when single equivalent antisecretory doses of F and R were given orally to histamine stimulated dogs, F exhibited 67% inhibition 24 hours post drug administration vs. only 2% for R. By the I.V. route however, duration of activity of F against a constant stimulatory dose of histamine in dogs was only slightly longer (1.3) than C.

In Heidenkain (vagally innervated) pouch dogs, F and C both competitively inhibited the secretory response of dimaprit, a specific H2 receptor aganist, whereas both induced an unsuromountable and thus non-compietitive antagonism of methacholine and pentagastion.

In gastric fistula cats, F, given s.c., was 38 and 5 times more antisecretory than C and R against histamine and 20 and 8 times against tetragastrin.

In chronic fistula rats, F and C inhibited basal acid output mainly by decreasing acid concentration; both also lowered pepsin output to a lesser extent. F was about 15 times more potent than C. In pylorus ligated rats treated orally, intraduodenally, and I.V., the ED50 antisecretory dose was similar and averaged 0.58 mg/kg.

No tolerance to the gastric antisecretory effect of F was seen in rats and dogs treated orally with subacute doses.

In rats treated p.o. with 3 mg/kg of F for 8 days, and "acid rebound" effect was noted 3 days after stop of treatment. In another study however, this rebound effect did not appear 1 or 3 days after repeated oral dosing of rats with 5 mg/kg b.i.d. for 30 days.

F inhibited cyclic AMP formation in the gastric mucosa of untreated and histamine stimulated rats, but mostly of the latter.

3) Antiulcer Activity;

F inhibited gastric ulcers induced in rats by a variety of agents or procedures (histamine, indomethacin, aspirin, cysteamine, stress, pyloric ligation) as well as or against duodenal ulcers induced with mepirizole. the ED50 of F ranged from 0.17mg/kg to 0.6 mg/kg and potency ranged from 17-44 times that of C. Effectiveness of F was greatest against histamine induced ulcers. Antacid (maolox) enhanced the antiulcer activity of F in rats.

4. Effect on serum gastrin:

In rats in which the acidity of the stomach was maintained through perfusion of HCl, F did not elevate serum gastrin whereas C did at equivalent antisecretory doses. No data are available on serum gastrin levels in animals treated with F alone.

5) Miscellaneous G. I. Effects:

In normal rats, F did not affect the histamine content of the gastric mucosa, but it did lower the mucosal level of endogenous PGE_2 and PGI_2 to a slight extent; C however lowered these prostaglandins to an even greater extent.

F did not influence propulsion of a charcoal meal in mice but it shortened gastric residence time in rats and dogs. In cats, F did not prevent the fall of transgastric electropotential difference which accompanies the administration of aspirin and which is considered to reflect disruption of the gastric mucosal barrier.

6. Cardiovascular Activity:

F exerted no effect on blood pressure, ECG, or respiratory rate in conscious dogs up to 30 mg/kg p.o. In the general toxicity studies conducted in dogs, no ECG or heart rate changes were noted in dogs treated orally with up to 2000 mg/kg b.i.d. for 30 days, up to 1000 mg/kg for 13 weeks, or 500 mg/kg for one year.

In spontaneously hypertensive rats, F had no effect on blood pressure at 10 mg/kg p.o.

Dogs injected I.V. with 1 mg/kg acutely displayed no effect on ECG or heart rate. However 10 mg/kg I.V. caused slight tachycardia and hypotension, and 30 mg/kg caused distinct tachycardia, hypotension, T wave elevation and increased respiration. The I.V. injection of 300 mg/kg acutely induced respiratory arrest, pronounced sustained hypotension, and finally death 20 minutes post drug.

F exerted no effect on the rate or contractility of the isolated G. Pig atrium.

In a six month I.V. toxicity study in dogs at 5, 25, and 100 mg/kg, reddening of mucous membranes possibly due to vasodilatation and significant tachycardia was noted at 100 mg/kg slight tachycardia only at 25 mg/kg, but no cardiovascular effects at 5 mg/kg.

7. Autonomic Reactivity:

Three mg/kg I.V. of F displayed no effect on muscarinic, nicotinic, histaminergic, H, or sympathetic alpha or beta receptors in dogs. It counteracted dimaprit induced hypotension in dogs through H_2 receptor antagonism.

8. CNS and Behavioral Effects:

F did not elicit any oral CNS effects at high oral doses (up to 2000 mg/kg b.i.d.) in mice, rats, rabbits, cats, or dogs other than retching or vomiting in dogs. It had no effect on locomotion or rotarod performance in mice treated with 100 mg/kg p.o., although 100 mg/kg I.V. reduced activity slightly in this species. Further, F had no effect on thiopentol induced sleeping time in mice or hexobarbital induced sleeping time in rats up to 100 mg/kg p.o. or I.V. whereas C prolonged sleeping time.

F had no effect on pentetrazole induced seizure in mice, displayed no non-narcotic analgesia in mice, nor interfered with morphine analgesia.

Doses of up to 10 gm/kg p.o. or 30 mg/kg I.V. had no visible effect on behavior in mice and rats. Further, F had no effect on metamphetamine induced stereotyped behavior in rats while C did have an effect. Condition avoidance behavior in rats was unaffected with up to 100 mg/kg p.o. but it was slightly impaired in squirrel monkeys at 3 and 9 mg/kg p.o. F exerted no EEG effects in immobilized cats up to 10 mg/kg p.o. Hippocampal after discharge in rabbits was unaffected up to 10 mg/kg I.V. or in cats up to 3 mg/kg I.V., but was delayed significantly in latter at 10 mg/kg. In cats injected I.V. with 3 mg/kg of F, 4% of the plasma concentration of drug was detected in cerebrospinal fluid. In dogs, a dose of 100 mg/kg I.V. elicited vomiting which was not preventable by metoclopramide.

9. Drug Interaction

In Vitro:

F and R demonstrated significantly less binding to Cytochrome P450 than C. In keeping with this, F and R did not display unusual U.V. spectra with microsomal preparations from uninduced and phenobarbital induced rats whereas, C did. Further, F and R had little effect on in vitro cytochrome P450 activity or Benzphetamine N-Demethylase activity with untreated or phenobarbital stimulated microsomes, whereas, C did. F and R had virtually no effect on the in vitro activity of microsomal 7-ethoxycoumarin O-Deethyllase activity with untreated phenobarbital, or 3 MC induced microsomes, whereas C did. F and R did not suppress 16 alpha, 7 alpha, and 6 beta hydroxylases of testosterone in liver microsomes of mice, whereas C did. Finally, F did not inhibit amenophyrine N-demethylase activity and diazepam metabolism in vitro, whereas C did.

In Vivo:

F did not delay the metabolism and excretion of diazepam, warfarin or propranolol in dogs, whereas C did judging from increased half-life, higher peak plasma concentrations, and greater AUC's of these drugs.

F and R did not increase the plasma concentration of antipyrine in rats, whereas C did significantly.

Sleeping time of pentobarbital was unchanged in rats pretreated with F for 14 consecutive days, but significantly reduced in rats pretreated with phenobarbital, a hepatic enzyme inducer. In addition, the phenobarbital-treated rats excreted more ascorbic acid in the urine and displayed larger livers than the F treated rats.

F did not affect hexobarbital sleeping time in rats, whereas C did so significantly.

10. Anti-androgenicity:

Castrated rats supported with exogenous testosterone showed no reduction in prostate or seminal vesicle weight when treated with 50 mg/kg p.o. of F for 7 days. The same model however showed significant reduction in the weight of these organs when treated with the same dose of C.

F did not inhibit in vitro the binding of testosterone to the androgen receptr present in the rat prostate cytosol.

11. ADME

a. Absorption

About 30-40% of an oral dose is absorbed in rats, dogs, and humans. In bile cannulated rats, 28% of an oral dose was recovered in the urine, 2.4% in the bile, and 70% in the feces. Hence, the bioavailability of F is moderate.

The bioavailability of type A crystals present in bulk material was essentially the same as type B crystals (presumably the early pilot batches).

In vitro, 21 to 27% of drug is bound to plasma protein in rat, dog, and human blood. In vivo, 15 to 22% of either F, C or R are bound to protein in the blood of human recipients.

In rats, the 1/2 life after oral dosing was 1.9 hour; peak plasma concentration was reached in about 2 hours.

In humans and dogs treated p.o. the half life was about 3 hours and the peak plasma concentration was reached in 3 hours.

Repeated p.o. or i.v. dosing of dogs showed no tendency for accumulation in the plasma.

b. Distribution:

In rats treated orally with a single dose, the levels of F were highest in the G.I. tract, kidneys, liver, submandibular glands, and pancreas in descending order. After i.v. administration the same order of distribution was found except that none was present in the G.I. tract. Little if any was found in the brain in either instance. All evidence of drug was absent by 24 hours post-drug.

Whole body radiographic studies of acutely-treated rats revealed only trace amounts after oral dosing (exclusive of the G.I. tract), but significant amounts in the liver, kidneys, G.I. tract, arteries, epiphyseal membranes, fasces, and uvea after i.v. dosing; drug disappeared in a short period of time and none was ever present in the brain or spinal cord.

Administration of drug p.o. or i.v. to pregnant rats showed only traces in fetal tissue, but significant amounts in the milk.

Multiple dose testing of rats for 21 days revealed slight rise in tissue levels of drug, but no significant accumulation; excretion pattern after 21 days (20% in urine and 70% in feces) was similar to that after acute dosing. Virtually no drug was detected in the brain.

Young rats injected i.m. with F from day 1 to day 28 of lactation showed relatively high levels of drug in tissues originally, brain included, but diminishing levels with time. Content of the brain was always less than that in other organs and nil after day 21. The descending order of distribution was kidney, liver, blood, heart and brain.

Young suckling rats nursing from mothers treated p.o. or i.v. on day 14 of lactation showed drug in liver and kidneys but none in the brain.

c. Metabolism:

Metabolism is very similar in rats, dogs and humans in that in each case 80% of absorbed drug is unmetabolized, the remaining 20% being metabolized to one specific product, the S-oxide. Almost all of the absorbed parent compound and its S-oxide derivative are excreted in the urine in each species. The structure of the S-oxide, which incidentally exhibits 1/270th the H_2 receptor antagonism of the parent, is as follows:

Famotidine S-oxide
(identical to F except for O attached to S atom)

the relative immunity of F to metabolism suggests that it will be virtually unaffected by hepatic first pass effect.

d. Excretion:

Excretion of F in rats, dogs, and humans is essentially the same. In each case virtually all of the absorbed drug is eliminated by the kidneys, a very small fraction being eliminated through the bile. This is true whether the drug is given p.o. or i.v.

12. Miscellaneous:

F had no effect on pancreatic or biliary secretion, hepatic blood flow, spontaneous G.I. motility, methacholine induced salivation, immediate hypersensitivity reactions, cellular or humoral immune responses or histamine induced asthma in guinea pigs.

Evaluation:

Famotidine (F), which is structurally related to tiotidine, has been clearly shown from pharmacological assays in vitro and in animals to be a very potent and very selective H_2 receptor antagonist and gastric antisecretory agent. Less certain is that the drug acts on the gastric H_2 receptor in a competitive way like cimetidine (C) and that it is somewhat longer acting in vivo.

In all of the assays, in vitro and in vivo, and regardless of route (p.o. or i.v.) or the secretory stimulant, F was invariably many times more potent than cimetidine(C) or ranitidine (R). For example, against histamine induced gastric secretion in dogs, orally administered F was 95 and 15 time more effective than C and R respectively. The single oral antisecretory ED50 dose of F in the latter model was only 0.03 mg/kg, which is 1/33 the human dose.

The nature of the antagonism was competitive against some H_2 receptors, non-competitive against others. For example, in assays involving gastric receptors (inhibition of dimaprit induced gastric secretion in Heidenhain pouch dogs, inhibition of adenylate cyclase activity and cyclic AMP formation in membrane fragments of guinea pig gastric mucosa), F displayed competitive inhibition qualitatively like that shown by C. However, in an assay that involved non-gastric H_2 receptors (inhibition of dimaprit induced tachycardia of the isolated guinea pig heart), F showed distinct non-competitive and unsurmountable antagonism, whereas C and R showed competitive easily reversible antagonism. In addition, F was shown to be tightly bound to the H_2 receptors in this model while C and R were loosely bound. Since F was always a competitive inhibitor in assays involving gastric systems, it is assumed that it will exert a competitive type antisecretory action in man similar to that observed with C.

The time course (duration) of gastric antisecretory activity of F was somewhat longer than R and C. For example, 24 hours after the oral administration of equivalent antisecretory doses of F and R to histamine stimulated dogs, 67% inhibition still remained with F, but only 2% with R. However, by the i.v. route in histamine stimulated dogs, the duration of antisecretory effect of F was only 1.3 times longer than C. It would appear then that F will be somewhat longer acting than R or C, but not extraordinarily so like omeprazole; 24 hour achlorhydria resulting from a single dose of F is quite unlikely despite the drug's remarkable potency.

The selectivity displayed by F was truly outstanding; whereas, only 0.03 mg/kg was required to demonstrate significant inhibition of gastric acid secretion in histamine stimulated dogs, hundreds times that dose showed no properties indicative of an H_1 receptor antagonist (conventional antihistamine), an anticholinergic or cholinergic, a histaminergic, an alpha- or beta-agonist or antagonist, a CNS stimulant or depressant, a tranquilizer, a behavior altering agent, or an allergenic compound. No cardiovascular or ECG effects were apparent in dogs after an oral dose of 30 mg/kg (1000 times ED_{50}).

Most incredible was the total absence of overt clinical reactions or serious toxicity in rats and dogs treated orally by gavage for 4 to 13 weeks with up to 2000 mg/kg b.i.d., a level which exceeds the ED50 in dogs by a factor of 133,333!

Based on the preclinical findings, will quite likely be devoid of anti-androgenic properties and not be prone to serious drug interaction problems. For example, like R, and unlike C, F did not bind significantly to cytochrome P450 enzymes of the liver in vitro and did not alter the pharmacologic activity, metabolism, or excretion of a number of C sensitive drugs (diazepam, warfarin, propranolol, pentobarbital, hexobarbital and antipyrine). Concerning anti-androgenicity, F did not influence the effect of exogenous testosterone in castrated rats, interfere with the in vitro binding of testosterone to androgen receptors, or reduce prostate or seminal vesicle weights in rats or dogs treated subacutely with up to 2000 mg/kg b.i.d.

We have no information in animals whether F elevates serum gastrin through induction of gastric hypoacidity. All that has been shown is that F does not increase serum gastrin in rats in which gastric acidity is kept normal by acid perfusion; this contrasts with C which raises serum gastrin under the same conditions.

One striking feature of the pharmakinetics of F is the almost identical way rats, dogs, and humans handle the drug. In all three species, F is moderately absorbed (30-40% of dose) is 20% bound to plasma protein, achieves peak plasma concentration in 2-3 hours, is slightly metabolized to just one metabolite, the S-oxide of the parent compound, and is almost all exereted via the kidneys (98% of absorbed drug via kidneys 2% via bile). This suggests that the pharmacological and toxicological results in animals are probably reasonably reflective of the drug's clinical potential.

The distribution studies showed the customary high concentrations in the kidneys and liver and negligible amounts in the brain and fetal tissue, but one peculiarity was the finding of high amounts of drug in the milk of lactating rats. This may explain why the growth of their nursing offspring tends to be depressed. Another noteworthy finding was the demonstration that, in newborn rats injected i.m. daily for 28 days, F passes the blood-brain barrier with decreasing efficiency until the 21st day, after which time no drug passes the barrier.

Concerning toxicity, the Yamanouchi Company and MSD have together supplied a wealth of animal toxicity data: acute studies in two species by all routes, numerous subacute, chronic, and reproduction tests by the oral route, oral carcinogenicity studies in mice and rats and a large battery of various mutagenicity assays.

As a whole, these data show F to be an astonishingly non-toxic and paradoxically inert compound, especially when one considers its extraordinary antisecretory potency (oral gastric anti-secretory ED50 in dogs is just 0.03 mg/kg and the daily human dose is only 1 mg/kg). For example, the acute oral LD50 of F in mice and rats was in the order of 4000 mg/kg when given in solution form and 8000 mg/kg in suspension form. In multiple dose studies, rats tolerated as much as 2000 mg/kg b.i.d. for 13 weeks and 1000 mg/kg for one year while dogs tolerated as much as 2000 mg/kg b.i.d. for 30 days and 500 mg/kg for one year. In these studies with doses far in excess of the HD, F appeared to be a rather inert compound in that it elicited no overt clinical reactions and no dramatic disturbances. The only indications of drug toxicity were proteinuria in rats and dogs at high doses, occasional elevations of SGPT in dogs, and alteration of chief cells, enlargement of the nuclei of these cells, and finally an increase in eosinophilic cytoplasmic granularity (ECG) of these pepsin secreting cells. Examination with electron microscope revealed only an increase in the density of these granules over that seen in the untreated animal. The threshold dose for this effect appeared to be about 2000 mg/kg p.o. and it was completely reversible within 16 weeks upon discontinuation of treatment. The sponsor conjectures that these chief cell changes may reflect reduced turnover of pepsinogen secondary to the drug's antisecretory effect, but this is difficult to reconcile with the observation that the drug still elicited these changes in rats subjected to continuous HCl perfusion of the stomach. However, the changes did not involve a change in the intracellular concentration of pepsinogen or ability of the cell to secrete pepsin.

One effect that was surprisingly absent in all of the animal studies was ECL cell hyperplasia in the gastric fundus. This gastrin dependent effect is characteristically seen in animals, especially rats, with potent long-acting gastric antisecretory agents (omeprazole, SKF-93479, Loxtidine, and BL-6341A). Perhaps F did not produce ECL cell hyperplasia because, despite its extraordinary potency and somewhat greater duration of action, its time course of antisecretory effect is still incapable of inducing sustained (24 hr.) achlorhydria and hypergastrinemia or anything comparable to it. This of course is a favorable finding because it tends to rule out a potential for inducing gastric carcinoid tumors which arise from hyperplastic ECL cells.

The various mutagenicity tests conducted on F showed it to be lacking in mutation potential. Following reaction with nitrite however, the reaction product (which likely included nitrosamines) was mutagenic against B subtilis strains M45 and H17.

The significance of the latter finding is doubtful however, since F was completely without carcinogenic potential in an oral carcinogenicity study of 92 weeks in mice and 106 weeks in rats up to 2000mg/kg/day in each case. Specifically, there was no evidence of gastric mucosal metaplasia, dysplasia, or neoplasia; there was no sign of the adenocarcinomas which appeared in the pylorus of rats treated for 6 months or more with structurally related tiotidine; nor was there any mention of ECL cell hyperplasia or carcinoid tumors in the gastric fundus. Finally, no carcinogenicity was suggested in any other organ, testes and liver included.

The reproduction studies conducted in animals provided essentially favorable results. Disturbances of reproductive parameters occurred only at high levels and appeared to be related to the sustained appetite suppressant properties of the drug. For example, the drug induced significant anorexia and sustained growth depression in pregnant rabbits at 200 mg/kg p.o. and above (but not at 100 mg/kg, 100 times HD). Some of the mothers that showed significant growth suppression at 200 mg/kg or above aborted their young and showed yellow livers at necropsy; also, the offspring of dams that did not abort gave birth to offspring that weighed less than corresponding controls. These effects, particularly the abortions, are no doubt indirectly due to prolonged starvation and not directly due to the drug. Supporting this is the fact that abortion never occurred during the drug treatment period, but later, (in the interval that separated termination of drug treatment and planned time of sacrifice of the mothers), and after virtual total anorexia had been in effect for some time. Also, abortion rarely occurred in a rabbit that did not show significant growth suppression.

Another disturbance possibly related to anorexia was the extended impaired growth of nursing neonatal rats. As suggested earlier, this may be attributed to the demonstration that F passes the blood-mamary gland barrier with ease in this species and accumulates in the milk and in addition passes the blood-brain barrier of neonates with relative ease for the 1st 21 days. The threshold maternal dose for neonatal growth depression was about 500 mg/kg. The persistence of the anorexia associated with F was reflected by the fact that weaned offspring continued to show growth depression for some eight weeks after separation from treated mothers.

In summary, based on the animal findings, Famotidine is predicted to be a very potent, very selective, long-acting and competitive H_2 receptor antagonist. The data also predict an unusually safe compound with a therapeutic index superior to cimetidine or ranitidine. It will likely compare to ranitidine and contrast with cimetidine in being devoid of anti-androgenicity and significant drug interaction complications. It should be like cimetidine and ranitidine and unlike metiamide in lacking a significant potential for agranulocytosis. Freedom from cardiovascular complications with oral use may be a unique advantage for F. Despite its extraordinary potency and somewhat longer duration of action, Famotidine does not seem to have any potential to cause sustained gastric achlorhydria, sustained hypergastrinemia, gastric ECL hyperplasia, or gastric carcinoids when administered once a day regardless of dose. In oral carcinogenicity studies of approximately 2 years duration in mice and rats up to 2000 mg/kg, (2000 times HD), it demonstrated no carcinogenic potential in any organ, the stomach, liver, and testes included.

In conclusion, Famotidine has been thoroughly investigated in animals and has clearly demonstrated efficacy and reasonable safety. Accordingly, this well-organized and very readable NDA (#19-462)by Merck Sharpe and Dohme for Pepcid(famotidine) Tablets is approvable from the preclinical standpoint.

The only recommendations offered are that the labeling:

1. warn against use by nursing mothers since in rats Famotidine accumulates in the milk, penetrates the blood-brain barrier of neonates with relative ease, and causes extended growth depression in nursing offspring.

2. suggest lowering of dose in patients with impaired kidney function since in rats, dogs and humans, absorbed drug is eliminated almost exclusively in the urine.

Pierre Deslauriers

Pierre Deslauriers, Pharmacologist

cc: Orig. NDA 19-462
HFN-110
HFN-110/CSO
HFN-110/PDeslauriers
HFN-102/VCGlocklin
HFN-345/GWJames
r/d init. PJDeslauriers,Act.Superv.Pharm.
cb:kg:rq:0705v:1-8-86

HFN-110 Dr Bachrach
HFN-110 Dr Stern

[redacted]

NOV 1 1984

September 13, 1984

Review and Evaluation of Animal Date
(Amendments of April 6, 1984)

The amendment supplies the following additional animal date:

1. Three month range-finding study in mice: Groups of 15 M and 15 F mice were gavaged once daily with MK-208 at levels of 0, 100-200, 400 700-1500, and 1000 mg/kg for 3 months in a study intended to find suitable doses for a carcinogenicity study.

   Results:

   Due to lack of toxicity, some dose levels were increased at five weeks. Viscosity limited the maximum dose to 2000 mg/kg. The drug was apparently very well tolerated at all levels, survival and growth being undisturbed. Necropsies were not done.

2. Ninety two week carcinogenicity study in mice: Groups of 50 M and 50 F Charles River mice were given MK-208 in suspension by gavage once daily at levels of 20, 200, and 2000 mg/kg/day (2000 times the daily human dose) for 92 weeks.

   Results:

   All treated groups performed as well as controls, the treated were like controls with respect to survival, growth, ophthalmoscopic exams, and gross and histologic findings except that diffuse distention of the glands of the fundus of the stomach was noted in 42% of the females at the top dose vs 11% among controls. There was no specific tumor that was statistically more prevalent in the test groups vs controls. There was no indication of carcinogenicity in either the stomach or testes. The only suspect finding was the occurrence of adenoma or adenocarcinoma of the lung in 31 of 100 low dose animals vs. 22/100 and 15/100 in the two control groups; however, the incidence at the mid and high dose was like the controls.

3. One hundred and six week carcinogenicity study in rats: Groups of 50 M and 50 F rats were gavaged with 20, 200, and 2000 mg/kg of MK-208 in suspension for 106 weeks. Two control groups each of similar number were used.

Results:

Again the test groups performed like controls. Morbidity among the males was slightly higher than controls at each test level and among the females as well at the top dose. For example, the percent of rats that died or were sacrificed before termination was 64%, 76%, 78% and 76% among the C,L,M, and H dose males and 42%, 48%, 52% and 72% among the respective females. Some of these deaths in the test groups were most likely due to accidental lung intubation considering the higher incidence of foreign body material in the lungs of animals at the upper two levels. Growth was unaffected and ophthalmoscopic exams were normal. Gross and histologic exams did not show carcinogenicity in any organ, the stomach and testes included. The only questionable finding was endometrial polyp in 3/50, 1/50, and 1/50 females at the high, mid, and low doses vs 0/100 control females, this tumor however was not statistically significant.
Non-neoplastic changes that were drug related included: glandular tissue distention in 5/50, 3/50, and 10/50 females from the low, mid and high dose levels vs 1/100 control females, nuclear enlargement of glandular mucosa in 9/100 and 26/100 from the mid and high doses vs 7/200 controls eosinophilic cytoplasmic granularity of zymogen chief cells in 23/100 and 49/100 from the mid and high doses vs 25/200 controls. The sponsor considers all of the foregoing changes as "physiologic alterations related to the pharmacologic activity of the test article, i.e. inhibition of pepsin turnover secondary to inhibition of acid secretion".

EVALUATION:

The ninety two week carcinogenicity study in mice and the 106 week carcinogenicity study in rats did not show MK-208 to be carcinogenic in either species tested approximately two yrs. with daily dosages ranging to 2000 mg/kg or 2000 times the human dose of 1mg/kg/day. It was notable that there was no evidence of carcinogenicity in either the stomach or testes.

Because some H2 receptor antagonists have produced stomach and testicular tumors near the end of a rodent's lifetime, it would have been preferable if these studies were lifespan studies. Since however they gave not even a suggestion of tumors in either organ after a fairly lengthy period of time (which extended over most of the animals' lifespan), the submitted studies appear to reasonably exclude the possibility of carcinogenicity.

Pierre Deslauriers

Pierre Deslauriers, Ph.D.

cc:Orig
HFN/110
HFN/110/CSO
HFN/110/PDeslauriers
cb/10/22/84/8628c
R/D: C.A.Resnick
Dr Bachrach
Dr. Stern

DIVISION OF CARDIO-RENAL DRUG PRODUCT
CHEMIST'S REVIEW #3

Date Completed: March 31, 1986

A. 1. NDA 19-462:

Sponsor: Merck Sharp and Dohme

Address: West Point, Penn 19486

AF #: 12-611

2. Product Name (s):

Proprietary- Pepcid

Nonproprietary- Famotidine

USAN- as above

Compendium- none listed

Code Name and/or number-
Refer to Chemist's Review [redacted]

3. Dosage Form and Route of Administration:
Oral tablets of 20 and 40 mg deveoped for marketing.

4. Pharmacological Category and/or Prinicpal Indications:

Potent, long-acting H_2 receptor antagonist (healer to peptic ulcers).

5. Structural Formula and Chemical Name:
See Chemist Review #1

B. 1. Initinal Submission: Receipt Date: 06-24-85
Filing Date: 08-22-85

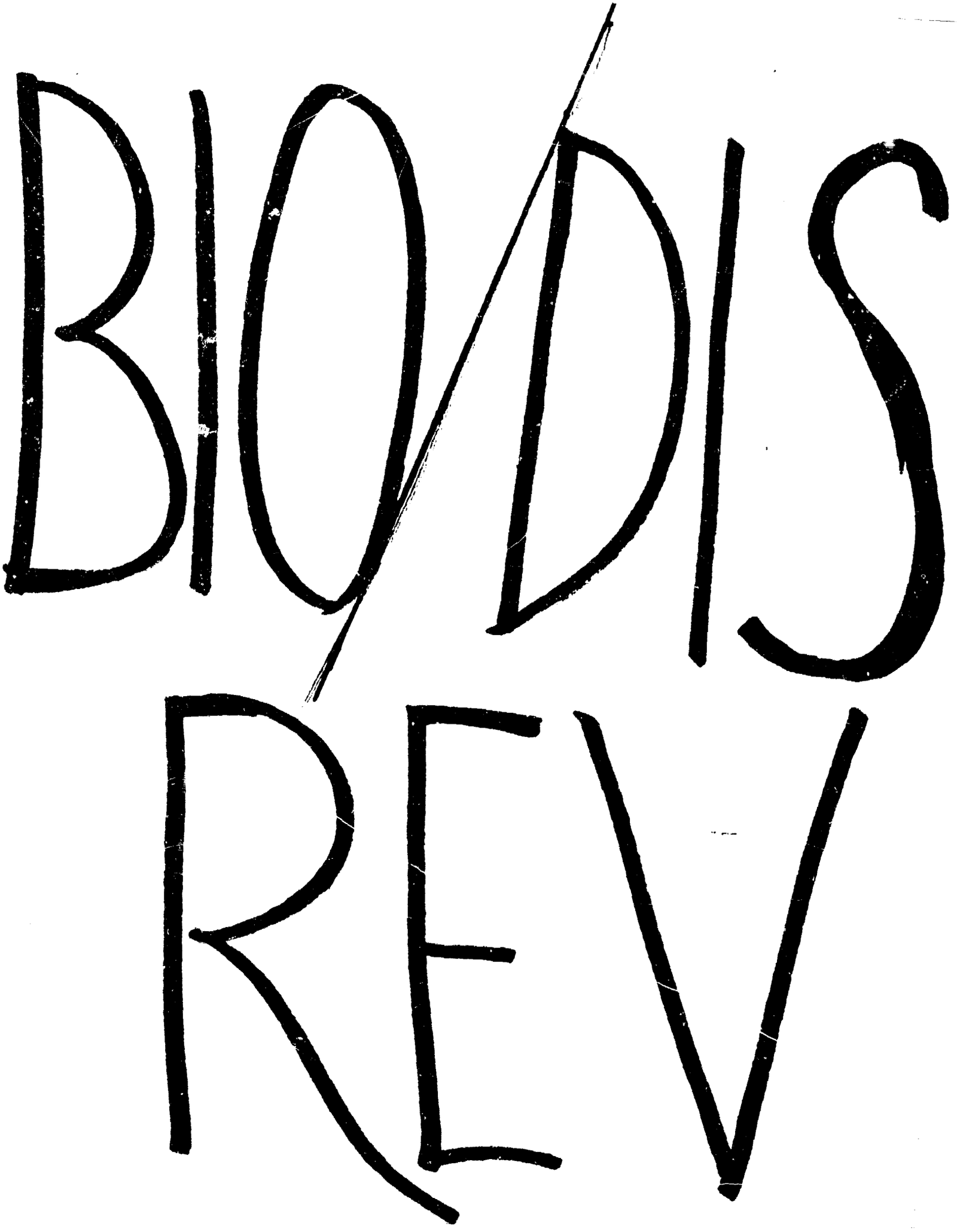
C. Remarks:

D. Conclusions:

This application is now considered to be approvable from the standpoint of manufacturing controls. The SBA has been changed to reflect this under the "Methods Validation" section.

Stuart Zimmerman
Stuart Zimmerman, Ph.D.
4-11-86

cc:
ORIG
HFN-110
HFN-110/CSO
HFN-110/SZimmerman/4/3/86
cb/4/3/86/0871v
R/D init RWolters/4/8/86


BIODIS
REV

F0[redacted]

Famotidine
Pepcid 20, 40mg tablets
NDA 19-462
Reviewer: See-Yan Lam
Wang[redacted]
14 S, 2D, 10

Merck Sharp & Dohme Res. Lab
West Point, PA 19486
Submission Date:
June 24, 1985
August 9, 1985
April 3, 1986

MAY 15 1986

Review of Pharmacokinetics and Bioavailability Studies

Famotidine is a H2 antagonist intended for treatment of acute duodenal and gastric ulcers, prophylactic therapy of duodenal ulcer, and Zollinger-Ellison Syndrome and other hypersecretory states. Chemically it is 3-(((2-(aminoiminomethyl)aminol-4-thiazolyl)methyl)-thiol-N-(aminosulfonyl)-propanimide. It exists in two polymorphic forms: Form A and Form B. It differs from the other two H2 antagonists in that it is a guanylthiazole derivative. Through the development of famotidine it is also referred to as MK-208, YM-1170 and L-643,341. The drug is licensed from Yamanouchi Pharmaceutical Company Ltd (Japan) by Merck & Company.

The following areas in different studies will be reviewed.

A. Human Pharmacokinetics:-

1. Single dose IV administration in healthy young subject.
2. Repeated IV administration in healthy young subject.
3. Single dose IV administration in healthy elderly subject.
4. Single dose IV administration in renally impaired patients.
5. Fate and metabolism in man.
6. Dose-proportionality following oral administration.
7. Protein binding.

B. Bioavailability:-

1. Effect of polymorphism.
2. Bioavailability of Pepcid tablets
3. Bioequivalence of other formulations used in clinical trials.
4. Effect of food and antacid.
5. Bioavailability in elderly subject.
6. Accumulation upon repeated oral dosing.

C. Drug interaction studies

D. Assay methodology

E. Dissolution.

Reference 12 Williams R.L. #42 - Clinical Study Report
An open, four-way crossover, single dose, comparative bioavailability study of MK-208 capsules 20mg, MK-208 tablets 20mg and 40mg, and 20mg intravenous preparation. (Study #42)

Objective:
1. To compare plasma levels and urinary excretion of MK-208 attained after the oral administration of a single 20mg or 40mg tablet, with a single 20mg capsule and with the intravenous administration of a single 20mg dose of MK-208.
2. To determine serum prolactin levels before and after the administration of MK-208 20mg intravenously to the volunteers.

Subjects:
Sixteen volunteers found healthy as judged by medical history, physical examination, standard EKG, and routine laboratory tests. All were within 10% of their ideal body weight for their age and height. Exclusion criteria included volunteers with history of renal or hepatic disease, cardiac or gastrointestinal disorder, history of allergy to drug or food, pregnant or lactating woman and has to be drug and alcohol free for 7 days.

Investigator/Site:
Roger L. Williams, M.D.

Drug/Design:
Open, single dose, four-way crossover design.
Four study periods of 3 days each. Minimum of 1 week washout period.

MK-208 IV 20mg - Lot C-K 711
MK-208 Capsule 20mg - Lot C-K 712
MK-208 Tablet 20mg - Lot C-K 713
MK-208 Tablet 40mg - Lot C-K 714

Dosing/Sampling:
Drugs were administered at 0 hour with 250ml of water, with the IV dosage administered as a bolus over one minute.

Blood samples (5mls) were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 and 36 hours. With intravenous administration, additional samples were collected at 5, 10, 30 and 40 minutes. Blood was collected at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, and 4 hours to determine prolactin levels.

Urine was collected at -1 to 0, 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, and 48-72 hours. A 20ml aliquot was saved for analysis.

Analytical Method:
HPLC
See review of analytical methodology.

Results:

Pharmacokinetic Parameters Mean (± S.D.)

	IV 20mg	20mg Capsule	20mg Tablet	40mg Tablet
Cmax (ng/ml)	--	78.70(37.17)	78.88(29.78)	109.29(41.62)
Tmax (hour)	--	2.2(0.9)	2.4(1.4)	2.3(1.4)
AUC0-36 (ng/ml-hr)	863.16 (245.04)	442.12 (184.49)	424.79 (101.86)	646.21 (252.31)
U0-72 (% dose)	66.7(14.8)	31.8(12.6)	27.5(9.1)	31.1(17.6)
Vcl,r (l/h)	18.63(7.17)	14.80(4.92)	13.04(3.56)	20.76(9.21)
F oral/F IV (95% CI - geometric mean		0.47 (0.40, 0.56)	0.43 (0.37, 0.50)	0.40 (0.34, 0.48)

Power to detect percentage difference

Percentage Difference	A vs B	A vs C	B vs C
10	0.24	0.16	0.21
15	0.49	0.31	0.43
20	0.76	0.52	0.69
25	0.93	0.74	0.88
30	0.99	0.89	0.98

A = 20mg capsule
B = 20mg tablet
C = 40mg tablet

Pharmacokinetic parameter following single IV dose of 20mg
(Plasma profile - Table 3)

Plasma clearance (ml/min)	463±160
Renal clearance (ml/min)	310±120
Non-renal clearance* (ml/min)	152±78
Half-life (hr)	2.83±0.99
Urinary Recovery (% dose)	66.8±14.9

*difference between plasma and renal clearance

Serum Prolactin levels (ng/ml)
before and after IV

	Time							
	0	.25	.5	1	1.5	2	2.5	4
Mean	19.58	11.76	11.45	10.37	9.5	7.88	9.26	11.24
SD	10.55	5.66	4.65	3.94	3.88	3.15	4.3	4.09

Discussion:
1. The relative bioavailability of the three oral dosage as compared to the intravenous dose by comparison of the geometric mean was 0.47, 0.43, and 0.40 for the 20mg capsule, 20mg tablet and 40mg tablet respectively.
2. The bioavailability of the 20mg capsule and tablet were similar based on statistical comparison of pharmacokinetic parameters.
3. The 40mg tablet resulted in less than proportional increase in Cmax and AUC(0-72) as compared to the 20mg tablet, however, the urinary recovery data suggested proportionality.
4. The renal clearance after the 40mg tablet was higher than after the 20mg capsule or tablet. The firm suggested that the renal clearance might be plasma concentration dependent though they stated there is insufficient data to support this statement.
5. The firm concluded that serum prolactin levels determined after IV administration of pepcid does not show a pattern of drug stimulated increase of prolactin levels.

Conclusions:
1. The relative bioavailability of pepcid is approximately 45%.
2. The bioavailability of the 20mg tablet and the 20mg capsule is similar and could be considered bioequivalent.
3. There does not seem to be elevation of serum prolactin levels after IV administration of pepcid.

The above study is acceptable.

Reference 15 DeSchepper P. #748 (Protocol #527)
A double-blind, placebo-controlled study to investigate the safety and tolerability of repeated intravenous doses of MK-208 in healthy subjects.

Objective:
1. To investigate the safety and tolerability of repeated IV doses of MK-208 when administered to healthy subjects.
2. To obtain preliminary information on plasma concentrations and urinary excretion of MK-208 when administered as repeated IV doses to healthy subjects.

Subjects:
8 subjects between 19-24 years old, 67-90kg, in good health by medical history, normal laboratory screen, physical examination and EKG. Exclusion criteria included drug or alcohol abuse, history of throbosis, renal insufficiency, allergies, psychiatric disorder, drink more than 8 cups of coffee per day and smoked more than 10 cigarettes per day.

Investigator/Site:
P.J. DeSchepper,

Drug/Design:
Double blind, placebo-controlled, repeated dose study (20mg BID at 8am and 5pm for 15 doses).
MK-208 (10mg/vial) - Lot #FC-M040

Dosing/Sampling:
Dose 1
Blood samples were collected at 0, 10, 20, 30 minutes and 1, 2, 4, 6, 9 hours post dose.
Urine samples were collected at -1-0, 0-2, 4-6, 6-9 and 9-24 hours postdose.
Dose 5, 6, 11 and 12
Blood - post dose (Cmin)
Dose 15
Blood samples were collected at 0, 10, 20, 30 minutes and 1, 2, 4, 6, 9 hours post dose.
Urine samples were collected at 0-2, 4-6, 6-9 and 9-24 hours postdose.

Clinical observation included EKG, blood pressure and heart rate, pain induration and hardness at injection site, physical examination, blood/urine laboratory data, and reporting of adverse experience were also conducted.

Analytical Methodology:
HPLC - see review of analytical methodology.

Results:(Table 5)

Plasma Clearance (ml/min)	313
Renal Clearance (ml/min)	259
Non-renal Clearance (ml/min)	54
Half-life (hr)	2.7
Urinary Recovery (% of dose)	82.9

Geometric mean and ranges of values are reported.

Discussion:
After repeated IV doses, the half-life remained in the same range as after a single IV dose. By comparison of the plasma clearance and renal clearance values after a single and multiple dosing, there seems to be a decrease in the mean values, however this is cross study comparison. Also the percentage of the dose recovered in the urine seems to increase.

The firm reported that no adverse reaction nor dramatic changes in physiological parameters were observed nor reported.
There was hardness, swelling and redness or local hyperaemia that occured in two of the six subjects.

Comment:
The above study is acceptable.

Reference 16 Martin B. #744 (Protocol #518)
A two-part, open study in healthy elderly subjects to examine the pharmacokinetic profiles of MK-208 when administered as a single intravenous dose and single oral dose (Part I) and repeated oral dose (Part II)

Objective:
To examine the pharmacokinetic profile of famotidine in elderly subjects after single intravenous and oral doses and repeated oral doses.

Subjects:
8 healthy subject over the age of 65 (65-74), in good health with no significant history of liver, kidney, cardiac, gastrointestinal or hematological disease, not grossly over or underweight, no clinically significant abnormal laboratory values, creatinine clearance of greater than or equal to 70ml/min/1.73m2, and not on any medication chronically.

Investigator/Site:
Bernard K. Martin, Ph.D.

Drug/Design:
Open, two part study. Part I is a crossover study.

Study part	Treatment	Dose of Famotidine	Route
I	A	20mg	Intravenous
I	B	40mg	Oral
II	C	40mg q12h for 9 doses	Oral

One week washout between part I and II.
Famotidine oral tablets 40mg - LOT GBC-L647
Famotidine IV (10mg/vial) - LOT GBC-L648

Dosing/Sampling:
Blood was collected at the following times after each treatment
IV - 0(predrug), 5, 10, 20, 40 minutes, 1, 2, 3, 4, 6, 9, 12 hours.
Oral - 0(predrug), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12 hours.
Blood was drawn at the above time following the single dose in part I and the ninth dose of part II.
Blood was also collected at 12 hours after the second, fourth, sixth and eighth doses in part II.
Urine was collected at the following time after each treatment.
-1-0, 0-2, 2-4, 4-6, 6-9, 9-12, 12-24, 24-48, 48-72 hours after the intravenous and oral doses in part I and after the ninth dose in part II.

Analytical Method:
HPLC
See review of analytical methodology.

Results: Table 8-10,

Pharmacokinetic of Famotidine in elderly after a single 20mg IV dose

Plasma clearance (ml/min)	233
Renal clearance (ml/min)	183
Non-renal clearance (ml/min)	54
Half-life (hr)	3.95
Total urinary recovery (% of dose)	77.3

Summary data and statistic from Part I
20mg IV vs 40mg PO single dose.

Parameter	Route	Mean	Median	Range	p-value (IV vs PO)
AUCO-oo (ng.hr/ml)	IV	1388±299	1347		greater than 0.2
	PO	1232±381	1058		
VCL,R (l/hr)	IV	11.6±4.1	10.7		greater then 0.2
	PO	12.4±5.9	11.0		
Urinary (% of dose)	IV	78.7±16.6	78.5		0.0001
	PO	34.7±14.5	34.7		

The AUC values were adjusted by actual dose/prescribed dose.

Summary data and statistic from Part II
(Single 40mg PO vs ninth BID 40mg dose)

Parameter	Dose	Mean	Median	Range	p-value (Dose 1 vs Dose 9)
AUCO-12 (ng.hr-ml)	1	1064±323	982		greater than 0.2
	9	1194±259	1115		
Cmax (ng/ml)	1	159±39	156		greater than 0.2
	9	181±54	172		
Tmax (hr)	1	2.8±1.1	2.5		greater than 0.2
	9	2.9±1.0	2.8		
VCL,R (l/hr)	1	12.4±5.9	11.0		0.09
	9	10.2±3.9	10.2		
UO-12 (% dose)	1	31.6±12.4	30.3		greater than 0.2
	9	30.2±10.2	30.3		
Bioavail (%) relative to IV	1	45.9±12.5	45.3		0.09
	9	38.9±8.9	39.7		

Trough levels (12 hours post dose) (Dose 1, 2, 4, 6, 8, 9)

Dose	Mean	Median	Range
1	32.6±11.5	27.3	
2	36.4±9.5	37.9	
4	46.7±14.8	48.5	
6	44.1±7.6	45.6	
8	46.6±14.6	48.8	
9	42.6±13.2	36.9	

Discussion:
1. From the trough level data, steady state appears to be reached with the 4th oral dose (40mg bid).
2. Urine data shows that the renal clearance of the data in all but one subject to be two fold greater than creatinine clearance value suggesting that tubular secretion involve in the overall renal clearance of the drug.

3. By comparison of the pharmacokinetic parameters in elderly and young subjects (between subject comparison); clearance, terminal half-life, AUC and Cmax appears to be lower in the elderly than in the young subject. However, the bioavailability of the drug in both population appears to be the same (oral bioavailability in the elderly = 40-45%). In general, there is reduced renal function in the elderly which could explain decrease in clearance.
4. The firm reported that the 20mg IV single dose or 40mg BID (for 9 doses) appears to be safe and well tolerated by elderly subjects.

Comments:
The above study is acceptable for the characterization of famotidine pharamcokinetics in the elderly.

Reference 17 Abraham, P., Keane, W.F. #404 - Clinical Study Report
An open study to assess the disposition kinetics and safety of MK-208 in patients with moderate to severe renal insufficiency.

Objectives:
1. To determine levels of MK-208 in blood and urine of patients with moderate to severe renal insufficiency after the administration of a single, intravenous dose of 10mg of MK-208.
2. To assess the safety of MK-208 in these patients by monitoring vital signs and laboratory tests before and after drug administration.

Subjects:
18 subject was enrolled in the study. (6 women, 12 men). (22 to 66 y.o.)
Patients were seleceted to meet the criteria of moderate to severe renal insufficiency which was unchanges as determined by serum creatinine and creatinine clearance tests which varied less than 20% in two or three evaluations for at least two months prior to the start of the study. They were divided into 3 groups based on their creatinine clearance.

	# of subjects	Creatinine clearance
Group 1	7	30-50 ml/min and serum creatinine greater than 3%
Group 2	5	10-30 ml/min
Group 3	6	0-10 ml/min (anuric patients on dialysis).

Investigator/Site:
Paul Abraham, William F. Keane, M.D.

Drug/Design:
Open, non-randomized design.
Famotidine IV (10mg/vial) - LOT C-L361

Dosing/Sampling:
At time zero, the patients was given a single IV infusion of famotidine at a constant rate over 1 minute.
10 mls of blood was obtained at 0, 2.5, 5, 10, 20, 40 and 60 minutes and at 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours from the beginning of the intravenous infusion.
Urine was collected at -12 to 0, 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48 and 48-72 hours after drug administration.
Starting 90 minutes before drug administration, three 30 minutes aliquots of urine were collected as baseline samples for determination of baseline creatinine and inulin clearance. Creatinine and inulin clearances were determined for eight 30 minutes intervals following drug administration.
Patients were required to drink 1500mls of water in the 24 hours prior to dosing and 60-120 ml of fluid every 30 minutes during the test period.
All chronic therapy for other medical conditions was maintained for at least one week before the study and during the study.

Physical examinations and routine laboratory tests (hemogram, SMA-12, urinalysis) and ECG were performed before and after drug administration.

Results:
(Table 9, 10, 11; Figs. 5, 6, 7, 8)
1. The relationship between renal function and plasma clearance (total clearance), renal clearance, non-renal clearance, plasma eliminatin half-life, initial volume of distribution, total area under the plasma concentration time curve and urinary recovery are shown in Figs attached. From the data and simple linear regression, the ollowing could be concluded:-

a. with increasing renal impairment, renal clearance of famotidine is decreased.
b. With greater degree of renal impairment, total AUC increased, while urinary recovery, plasma clearance and initial volume of distribution decreased.
c. Non-renal clearance of famotidine is independent of renal function.
d. With increasing degree of renal impairment, plasma elimination half life is increased.

2. Mean values for creatinine clearance and inulin clearance shows that there were no significant changes before and after drug administration.

	Creatinine clearance	Inulin clearance
Before	38.8±18.6	27.2±14.1
After	36.5±15.2	27.3±10.5

3. By comparison of the data obtained from renal insufficiency patients, the half life of famotidine ranged from hours which compares to ranges of and in young and elderly subjects. (cross study comparison).

Discussion:
1) Half life of famotidine is increased in patients with renal insufficiencies. With decreasing creatinine clearance, there is a corresponding increase in famotidine elimination.Time.
2) The non-renal elimination of famotidine is not affected by renal insufficiencies.
3) Creatinine and inulin clearance is not affected by an acute IV administration of famotidine.
4) The above data agrees with previous finding of Yamanouchi. (Table 1)

Comments:
The above study is acceptable for the characterization of the pharmacokinetics of famotidine in patients with renal insufficiencies.

Reference 19 Rotmensch, H. #40-Clinical Study Report
An open study in four healthy volunteers to determine the absorption, distribution, metabolism and excretion of 20mg MK-208 labeled with C-14 (20uCi) administered orally.

Objective:
To investigate the levels of MK-208 and metabolites in blood, urine, and feces after the administration of an oral dose of 20mg of MK-208 labeled C-14 to healthy volunteer.

Subjects:
4 healthy male between the ages of 23-28 (mean 26), and weighing between 125.5-186 (mean 158.6) completed the study. Physical examination and standard laboratory blood and urinary tests were performed before and after drug administration.

Investigator/Site:
Heschi Rotmensch, M.D.

Drug/Design:
Open label, single dose study.
20mg of C-14(20uCi) labeled MK-208 was diluted with 50mls of purified water and ingested. 50mls of water was used to rinse the cup, and the content ingested.
200ml of water was given at 0, 3, and 6 hours after drug administration to ensure adequate hydration.
C-14 labeled MK-208 Lot # C-K023
Purified Water Lot # C-K024

Dosing/Sampling:
10ml of blood was collected at 0, 20, and 40 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after drug administration.
Fractional urine was collected before and at 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-72, 72-96, and 96-120 hours after drug administration.
All feces was collected up to 96 hours after drug administration.

Analytical Method:
HPLC analysis, Scintillation counting.

Results:
Tables 12-15.

Subject	1	2	3	4
% of the dose excreted				
URINE (0-120 hour)				
Mean ± SD	38.00±14.67			
Unchanged drug (0-24 hrs)				
Ratio of MK-208/ Total radioactivity excreted				
FECES (0-96 hour)				
Mean ± SD	50.58±21.07			
Grand Total				
Mean ± SD	88.34±11.40			

Discussion:
MK-208 is incompletely absorbed after oral administration. From the plasma concentration data, Cmax is reached between 1 and 3 hours after oral administration (Cmax 66.54+20.94, Tmax 1.4+0.5). Parent compound could be found in the plasma until 6 to 8 hours after oral administration. From the data, urinary excretion accounts for 24 to 57% of the dose, with 50 to 90% being the unchanged parent compound. Fecal excretion accounts for 28 to 79% of the dose administered. The primary metabolite found from HPLC extraction was the MK-208 sulfoxide.

Comments:
The above study is acceptable.

Reference 20 Zinny, M.A. #1 - Clinical Study Report
A double-blind, single rising dose, placebo controlled study to determine safety, tolerability, and dose-propertionality of blood and urine levels of MK-208 (L-643,341) administered orally to healthy volunteers.

Objective:
The objectives of this study were a) to determine the safety and tolerability of MK-208 when given in single, oral rising doses from 5 to 40mg to healthy volunteers, b) to determine the blood and urine level attained with the doses employed, and c) to assess the effect. if any, of the administered doses on serum gastrin and prolactin.

Subjects:
15 volunteers, mean age-29.2 (19-51), mean weight-160.2 lbs (128-215), judged to be healthy by their history, physical examination, laboratory tests and EKG, who had not taken any other medication within one week prior to the study participated.

Investigator/Site:
Miguel A. Zinny. M.D.

Drug/Design:
Double blind, single, rising dose, placebo-controlled, complete block study.
Lot # C-H348, for 5, 10, 20, 40mg MK-208 and placebo capsules.

Dosing/Sampling:
Following an ovenight fast, volunteers received a single dose of the MK-208 in increasing strength with placebo control randomly interspered as one of the treatment periods. Four hour after administration, the volunteers resumed a normal diet. One week minimum washout period.
6 mls of blood was collected at 0, 0.5, 1.25, 2, 3, 4, 6, 8, 10, 12, and 24 hours after dose administration.
Additional blood was also collected at 0 and 4 hours for assay of serum gastrin and prolactin level.
Urine was collected at -1-0, 0-2, 2-4, 4-6, 6-8, 8-12. 12-24, 24-36, and 36-48 hours.
Vital signs (BP, pulse and temperature) were measured at 0, 2, 4, 8, 12 and 24 hours post dosing.
Adverse reaction were questioned at 0, 0.5, 1, 2, 4, 8, 12 and 24 hours post dosing.

Analytical Methodology:
Not specify. Detection limit was reported to be 5ng/ml.

Results:
Table 16, 17. Fig. 10

Vital signs - There was no drug related effects on blood pressure, pulse rate or body temperature.
Laboratory Safety - There was no change in blood, blood chemistry, urine, fasting blood sugar, or EKG.
Serum Gastrin and prolactin -
Mean gastrin levels were significantly higher 4 hours after treatment with 20 and 40mg doses. Gastrin levels was reported to increase with increasing doses of MK-208
There was no drug related effect on serum prolactin.

	5mg	10mg	20mg	40mg
Cmax (ng/ml)	14.0±5.7	32.7±11.0	43.4±17.7	75.5±28.6
Tmax (hr)	2.3±1.1	1.9±0.7	2.3±0.9	1.9±0.8
AUC (ng-hr/ml)	68.94±42.58	183.26±86.34	281.19±125.34	482.28±181.20
Urinary recovery (% of dose)	27.5±13.6	27.7±8.5	23.7±6.7	19.5±5.3
Renal Clearance (Harmonic mean)	294	227	276	263
Half life estimated from urinary excretion	2.5±1.0	2.6±0.8	2.6±0.9	2.6±0.6
Bioavailability relative to 40mg dose based on urinary recovery	1.21	1.51	1.17	-----
95% C.I.	0.693,1.57	1.14,2.01	0.997,1.38	
Posterior Probability at 20%	0.593	0.078	0.806	
25%	0.777	0.170	0.952	
Power to detect a 20% difference	0.417	0.371	0.819	
25% "	0.616	0.556	0.959	
30% "	0.798	0.800	0.996	

Discussion:

Statistical analyses performed by the firm showed the following:-

Significant difference was observed for AUCs ($p<0.01$) and Cmaxs ($p<0.05$) as doses increase. There was no significant difference in Tmax.

The percent of dose recovered in urine was significantly lower ($p<0.05$) for 40mg than for 10mg or 5mg. Urinary excretion showed a significantly greater amount of MK-208 being excreted after 40mg dose (p 0.01) than after other doses, and excretion after 20mg greater than after 5mg through 12 hours.

Renal clearance was significantly lower for 10mg than for 5mg but there was no differences for 20 and 40mg from either 5 mg or 10mg.

No significnat difference was observed for terminal half lives amoung 10, 20 and 40mg.

The bioavailability of each dose relative to 40mg was calculated based on urinary recovery and the ratio of 20mg to 40mg was significantly greater than unity.

The posterior probability that the true mean difference in bioavailability relative to 40mg was less than 20 and 25% is shown above.

The power of detecting 20%, 25% and 30% between 40mg dose and other doses are also shown above.

(Power and posterior probabilities were calculated from the log-transformed bioavailability ratios according to the methods of Rodda and Davis, Clinical Pharmacology and Therapeutics Vol. 28, No.2, pp. 247-252, Aug 1980.)

Conclusion:
The firm concluded the following:-

Comments:
From the AUC data, the data suggest deviation from unity and disproportional increase in AUC as the dose increase. However, the data also shows wide intersubject variability. Dose proportionality calculation on AUC data performed by the Division of Biopharmaceutics also shows similar inter and intrasubject variability as observed in the calculation by urinary data. This variability could be associated with formulation factors or the physical properties (solubility) of the drug and also incomplete absorption of the drug. Famotidine was shown to have highly pH dependent solubility profile. (p977, Vol. 1.24 of this submission)

Solution	Solubility (mg/ml) at 20C
pH 3 Citrate buffer	
pH 4 " "	
pH 5 " "	
pH 6 Phosphate buffer	
pH 7 " "	
pH 8 Borate buffer	
pH 9 " "	

The pKa for famotidine (MK-208) is 7.1.

The study is acceptable though the question of dose proportionality of the drug is not quite answered.

Reference 21 Lin, J.H., Kanovsky, S.M. Merck & Co., 3/4/85
Protein binding of MK-208 in human plasma

Objective:
To investigate the protein binding of radioactive and non-radioactive MK-208 in human plasma.

Investigator/Site:
Lin, J.H., Kanovsky, S.M.
Merck & Co.

Methods:
Non-radioactive - Subject plasma samples from a clinical study (M.A. #59) was pooled within individual subjects across several time periods. MK-208 binding was studiesd by equilibrium dialysis. Dialysis was conducted at 37C against an isotonif buffer solution of 0.05M phosphate and 0.07 NaCl, pH 7.4 for 4 hours. The method of analysis for MK-208 was HPLC. The percentage of bound fraction (fb) was calculated by:-

$$\%, fb = \left(1 - \frac{C\ buffer}{C\ plasma} \right) \times 100$$

C buffer, C plasma being drug concentration in buffer and plasma.

Radioactive - Radiolabeled drug was added to the plasma component in volumes equal to or less than 1% of total volume. After equilibrium was reached, aliquots from buffer side and plasma side were mixed with 15mls of pcs (phase combing scintillation) and measure by liquid scintillation counting.

Results:
Table 18
Non radioactive

Concentration (ng/ml)	Bound Fraction (%)

Radioactive

Concentration (ng/ml)	Bound Fraction (%)

Conclusions:
On average, about 17% of the drug was bound to plasma protein. From the data it could be shown that there was some intersubject variation, but there does not seem to be a concentration depeidence plasma protein binding for MK-208 for the range of ng/ml.
It could be concluded that alteration in plasma protein binding would not altered the disposition pharmacokinetics of MK-208.

Comments:
The above study is acceptable for the investigation of plasma protein binding of MK-208.

Reference 11 Yamada, S, Imasaki, H, Nakamura, E.
Comparison between the bioavailability of Type A crystal famotidine and that of Type B crystal famotidine in dogs and human.

Objective:
Study of the physicochemical properties of famotidine demostrated that there were 2 crystal forms of famotidine, A and B, which were slightly different in their properties. The bioavailability of the 2 different forms were investigated in a cross over study by administering 20mg of the drug in a capsule form to dogs and human.
NOTE: The data from the animal portion of the study will not be reviewed.

Subjects:
12 volunteers, judged in good health by physical examinations were selected to participate in the study.

Investigator/Site:
Yamada, S, Imasaki, H, Nakamura, E.

Drug/Design:
Cross over, latin square design (two groups of six), with 1 week washout between treatments.
20mg capsule (Type A crystal) - Lot KYC-1
20mg capsule (Type B crystal) - Lot KYC-2

Dosing/Sampling:-
Volunteers were fasted overnight (at least 10 hours) and were given 20mg capsule with 100mls of water.
Bloood samples were collected at 0, 1, 2, 3, 4, 6, 8, 10 and 12 hours after administration.

Results:

	TYPE A crystal	TYPE B crystal
Cmax (ng/ml)	67.2±4.5	72.3±5.3
Tmax (hr)	2.67±0.22	2.83±0.32
AUC0-12 (ng-hr/ml)	338.5±30.1	335.8±31.4
T1/2 (hr)	2.93±0.16	2.82±0.26

(Mean±SE)

The data was compared by t-test, which demonstrated no significant difference in plasma levels at different time points, AUC and Cmax.

Conclusion:
The firm concluded that based on the above study, the two crystal forms did not differ significantly in the above pharmacokinetic parameters.
Similar results was observed in the animal study.

Comments:-
The above study is acceptable in demonstrating that the two crystal form of famotidine (MK-208) did not show statistically significant difference in the pharmacokinetic parameters considered.

Reference 23 Ryan, J.R. #52 - Clinical Study Report
An open two-way cross over, single oral dose bioavailability study of MK-208 tablets: 20mg (U.S. formulation) and MK-208 (Japanese formulation)

Objective:
To compare plasma and urinary levels of famotidine attained after the oral administration of a single 20mg tablet (MSDRL formulation, US) and after a single 20mg tablet (Yamanouchi formulation)

Subjects:
Sixteen volunteers weighing within ±10% of their ideal body weight and height for their age (mean age -32.9, mean weigth 166 lbs) and in good health based on history, physical examination, routine laboratory tests and EKG participated.

Investigator/Site
Jerome Ryan, M.D.

Drug/Design:
Open, single dose, randomized two-way crossover study.
Famotidine (MSDRL, US) - Lot C-L065
Famotidine (Yamnouchi, Japan) - Lot C-L066

Dosing/Sampling:
Drug was administered at approximately 8am on study day with 250mls of water. At 1, 3, and 6 hours after drug administration, they were asked to drink 250ml of water to ensure adequate hydration.
10mls of blood was collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 and 36 hours.
Urine was collected at -1-0, 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, and 36-48 hours.
Physical examination and laboratory tests were performed pre and post test.

Results:

	MSDRL formulation	Yamanouchi formulation	Treatment Comparison
Cmax (ng/ml)	68.1±21.8	66.9±16.7	NS
Tmax (hr)	2.0±0.7	2.5±0.6	$p < 0.05$
AUC 0-36 (ng-hr/ml)	416.1±137.8	403.2±123.0	NS
V cl r (l/hr)	15.3±4.2	15.0±6.1	NS
U 0-48 (% dose)	33.8±15.79	30.5±11.92	NS
FM/FY ratio of geometric means (95% CI)	1.054 (0.91, 1.22)		

Parameters	Posterior Probability	Power
Cmax	0.99	0.81
Tmax	0.37	0.77
AUC 0-36	0.99	0.87
U 0-48	0.79	0.35
FM/FY	0.97	0.78

Conclusion:
Urinary data - No significant difference was observed for percent of the dose excreted in 48 hours, or the mean renal clearance between the two formulations.
Plasma data - No significant difference was observed for Cmax and AUC for the two formulations, however, there was a significant difference in Tmax (2.0 hours vs. 2.5 hours).
The mean relative bioavailability calculated was not significantly different (1.054, 95%CI - 0.91, 1.22).
The percent of the dose from urinary recovery from both formulation was not significantly different.
From the urinary data, the clearance of famotidine is approximately 161/hr, which exceeds the glomerular filtration rate, which suggests that a tubular secretion process is involved in the renal excretion of MK-208.

Comments:
The difference in the Tmax of the two formulation of MK-208 could be attributed to the difference in dissolution of the two formulation. At the end of 30minutes the US formulation had 105% dissolved, whereas the Japanese formulation had 85% dissolved. (Formulation and physicochemical properties of the two formulation could be found in Table A).

The above study is acceptable in demonstrating that the two formulation of MK-208 is equivalent in the pharmacokinetics parameters considered.

Bioequivalence of other formulations used in clinical trials

The firm reported that besides the pepcid tablets, two additional famotidine formulations were used in pivotal studies - dry filled capsules which were used in early clinical trials and sugar coated famotidine tablets used in clinical trials in Japan. A list of these studies could be found in the attached pages.

The bioavailability of these two formulation relative to pepcid tablets were reviewed in the following which has been reviewed.

Reference 12 Williams R.L. #42 - Clinical Study Report
An open, four-way crossover, single dose, comparative bioavailability study of MK-208 capsules 20mg, MK-208 tablets 20mg and 40mg, and 20mg intravenous preparation. (Study #42)

Reference 23 Ryan, J.R. #52 - Clinical Study Report
An open two-way cross over, single oral dose bioavailability study of MK-208 tablets: 20mg (U.S. formulation) and MK-208 (Japanese formulation)

Summary of these data could also be found in Table 23, 24.

Reference 24 Kann, J. #47 - Clinical Study Report
An open, randomized three-way cross over single dose study to assess the effect of an antacid on the bioavailability of MK-208 and a standard meal on the bioavailability of MK-208 when each is administered concurrently with MK-208.

Objectives:
To compare plasma levels and urinary excretion of MK-208 attained after oral administration of a single 40mg tablet given alone or concurrently with a liquid antacid (Mylanta II, 10ml) or a standard breakfast meal.

Subjects:
24 men (age 21-40 years, mean 28±5, weighing 161.4±22.5 lbs) within 20% of the ideal body weight and in good health based on history, physical examination, routine laboratory tests and EKG participated.

Investigator/Site:
Jules Kann, M.D., Ph.D.

Drug/Design:
Open, single dose, randomized three-way cross over design. Minimum washout period of 1 week between treatments.
Famotidine 40mg - Lot C-L163
Mylanta II - Lot C-L153A

Standard breakfast - 4 ounces of orange juice, one individual size bowl of Special K cereal, 130ml low fat milk, and one fruit danish with one pat of magarine.

Dosing/Sampling:
Subjects were requested to fasted since midnight before the study day. 250mls of water was administered 1.5 hours before treatment administration (treatment started at approximately 8am).
Treatment A -
Tablet was administered with 150mls of water followed by 250mls of water 15 minutes later.
Treatment B -
10mls of Mylanta II (administered by syringe) was administered first followed immediately by the tablet given with 150mls of water. 250mls of water was given 15 minutes later.
Treatment C -
The meal which included 250mls of fluid was eaten first and was followed immediately by the tablet given with 150mls of water.
Additional 250mls of water was ingested at 2, 4, 6 hours after administration to ensure hydration.
10 mls of blood were drawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 and 48 hours after drug adminsitration.
Urine was collected the first day of each period, and also at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36 and 36-48 hours after drug adminstration.

Normal diet was resumed at 12 noon on the study days. No specific dietary instructions were given, except all subjects received the same meals.

Results:

	Treatment A 40mg MK-208 alone	Treatment B 40mg MK-208 with antacid	Treatment C 40mg MK-208 with food
Cmax (ng/ml)	81.09±54.25	60.83±21.62 *	81.55±29.60
Tmax (hr)	2.62±1.19	2.24±0.79	2.44±0.63
AUC (ng-hr/ml)	443.3±249.2	355.0±125.1	434.8±145.9
Urine recovery			
(mg)	9.87±4.29	8.81±2.91	11.34±2.99*
(% dose)	24.82±10.79	22.18±7.31	28.52±7.51*
Cl renal (l/hr)	25.8±10.5	27.8±11.6	28.5±11.6
Rel. Bioavailability			
(geom. mean)	------	0.900	1.141
95% CI	------	0.703, 1.151	0.932, 1.396

* significantly different from MK-208 alone, P 0.05
All other parameters were not significantly different.

The firm recalculated the data excluding Subject 12 and 16 as outliers. (Table B).

Antacid

Plasma data -
The mean Cmax value was reduced by 25% (significant different, p 0.05) when antacid was administered concurrently. However if subject 12 and 16 were eliminated from the analysis, the means were no longer significantly different. (70% power to detect a 20% difference) Individual values shows that 5 of the 17 subjects had more than a 20% reduction whereas 2 subject had an increase of 20% of more.
Tmax was achieved 23 minutes faster when antacid was administered with MK-208, however the difference was not significant. This conclusion was not changed with the exclusion of data from subject 12 and 16.
A 20% reduction in AUC value was observed when antacid was coadministered with MK-208. This difference was not statistically significant. With the exclusion of subject 12 and 16, the reduction in AUC value was less than 10%.
In general, all plasma time points were lower when antacid was coadministered with MK-208.
Urine data -
No significant difference was found in the cumulative urinary recovery or renal clearance of MK-208 when antacid was coadministered. Power to detect 20% difference for the above parameters were 50% and 82%. With the exclusion of subject 12 and 16, the power changed to 63.5 and 73.9.

Food

Plasma data -
No significant difference in Cmax was found when MK-208 was given together with food. However with the exclusion of subject 12 and 16, there was a significant increase in Cmax (19%) when MK-208 was given together with food. There was no significant difference in Tmax. However, Tmax was achieved 10 and 21 minutes sooner with food when subject 12 and 16 were included or excluded.
AUC data shows no significant difference whether subject 12 and 16 data was included or not. Power was low (45.8 and 49%) to detect a 20% difference.
Plasma time points shows that plasma level was lower at 0.5 hours when food was coadministered. After 1 hour, plasma level was either the same or higher with food.
Urine data -
Urine recovery of MK-208 was significantly increased with food. Increase was found to be 15% ($p < 0.05$) and 30% ($p < 0.01$) when subject 12 and 16 was exluded. Renal clearance was not significantly different with food.

Discussion:
Antacid - When MK-208 was given with antacid, a significant decrease in Cmax is observed. However, when subject 12 and 16 were excluded, there was no significant difference. No significant difference was observed for all the other pharmacokinetic parameters considered. The relative bioavailability of MK-208 was not significantly different with antacid whether the data from the above two subjects were excluded or included.
Food - Significantly higher recovery of MK-208 was found when it was given with food. Cmax was also significantly higher with food when the data from subjects 12 and 16 were excluded. No significant difference was observed for all the other pharmacokinetic parameters considered.

Conclusion:
The firm also stated that:-

Comments:
The above study is acceptable for demonstrating the effect of food and antacid on MK-208. The effect of antacid and food should be included in the labelling of the drug. The following statements that was used in the firms conclusion:-

1. Coadministration of MK-208 and food may result in a small increment of its bioavailability.
2. Coadministration of MK-208 with antacid may result in a marginal decrease of its bioavailability.
3. MK-208 may be administered therapeutically with food or antacid.

may be used as acceptable labelling.

The following are reviews of drug interaction study of famotidine.

Reference 25 Williams, R.L. #48 - Clinical Study Report
An open-labled, randomized two-way cross-over, single dose study to assess the effect of MK-208 and of cimetidine on the disposition of intravenous theophylline.

Objective:
1. To examine the effect(s) of repeat doses of cimetidine and of MK-208 on the plasma kinetics of theophylline given as a single intravenous dose.
2. To examine the plasma and urinary levels of MK-208 after single and repeated doses.

Subjects:
10 subjects, 22 to 32 years old (mean - 24.7) within 20% of the ideal body weight and in good health based on history, physical examination, routine laboratory tests and EKG participated.

Investigator/Site:
Roger L. Williams, M.D.

Drug/Design:
Open label, randomized two-way cross over study.
Each study period was 9 days duration and was divided into 3 parts.
Part 1 - 2 days - Baseline aminophylline (5mg/kg IV) administered and plasma and urine collected to establish baseline theophylline level.
Part 2 - 1 day - no drug washout period.
Part 3 - Either famotidine 40mg bid or cimetidine 300mg qid was administered and plasma and urine collected to establish single and multiple dose plasma and urinary levels of famotidine only. On the 4th day of drug administration aminophylline (5mg/kg IV) was given concomitantly with famotidine or cimetidine. Plasma and urine was collected for both drugs group for 48 hours.
Minimum of 7 day washout period.
Famotidine - Lot C-L347
Cimetidine - Lot C-L348
Aminophylline - No lot# - Investigator's pharmacy stock.

Dosing/Sampling:
Theophylline - On Day 1 and 7 of each study period, 5mg/kg of aminophylline was prepared and administered by IV pump over 20 minutes. 200ml of water was taken at time 0 and at 2 and 4 hours after drug administration. 3mls of blood was drawn at 0, 10, 20 minutes (end of IV infusion) and at 5, 15, 30 minutes and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours after infusion. After the 2nd administration of aminophylline, additional 5 mls of blood was drawn at the end of 20 minutes infusion period and at 1, 2, 4 hours for assay of cimetidine or famotidine. Urine was collected at -1-0, 0-2, 2-4, 4-6, 6-12, 12-24, 24-48 hours following aminophylline administration.
Famotidine/Cimetidine - Part 3 - Famotidine 40mg bid or Cimetidine 300mg qid was administered for 5 days. During famotidine dosing period, blood and urine samples were collected to determine single and multiple dose kinetics of famotidine.

5ml of blood was collecteu at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hours for evaluation of single dose kinetics adn repeated before the fifth dose for evaluation of multiple dose kinetics.
Urine was collected at 0-2, 2-4, 4-6, 6-12 hours following first and fifth dose.
Subjects were fasted from midnight to 12 noon before aminophylline administration. No xanthine containing food were allowed 24 hours before and after adminstration of aminophylline. One 1 ounce of 80 proof alcoholic beverage was allowed per day.

Results:

Theophylline Pharmacokinetic Variable		MK-208 Day 1 before	MK-208 Day 7 during	MK-208 change	Cimetidine Day 1 before	Cimetidine Day 7 during	Cimetidine Change	Treatment Comparison Change
TBC (ml/min)	mean	58.1	61.4	3.3	57.6	39.5	-18.1**	P 0.01
	S.D.	20.7	21.7	2.1	21.8	9.5	17.2	
T1/2 (hr)	mean	9.1	9.8	0.7	9.3	12.2	2.9	p 0.05
	S.D.	..0	2.5	2.2	2.4	1.7	2.4	
Vd (L)	mean	43.6	48.7	5.1*	42.9	40.8	-2.1	p 0.05
	S.D.	9.7	10.9	6.5	6.1	7.1	6.1	
Urinary Recovery 0-48 hour (mg)	mean	44.5	45.7	1.2	45.9	55.0	9.1	NS
	S.D.	12.9	17.4	19.5	12.4	17.2	25.2	
Urinary Recovery 0-48 hour (% dose)	mean	10.4	10.7	0.3	10.7	12.5	1.8	NS
	S.D.	2.7	3.7	4.7	3.4	2.1	5.0	
Renal Clearance (ml/min)	mean	6.8	7.1	0.3	7.2	6.5	-0.7	NS
	S.D.	2.0	2.1	3.1	2.3	1.9	3.4	

*, ** significant change from theophylline alone to during combination treatment, * p 0.05, ** p 0.01
NS - no significant between treatment differences were observed.

Famotidine levels after single and multiple dose

	Single dose mean	SD	Multiple dose Mean	SD	single vs multiple dose
Cmax (ng/ml)	192.6	78.8	192.8	78.9	NS
Tmax (hr)	1.6	0.7	1.3	0.5	NS
T1/2 (hr)	3.1	0.5	3.3	0.6	NS
AUC 0-12 (ng-hr/ml)	954.8	408.8	960.6	350.2	NS
Urine recovery 0-12 (% dose)	22.3	7.7	23.9	10.9	NS
Cl renal (l/hr)	10.1	3.4	10.4	4.0	NS
Cmin (ng/ml) Dose 1	17.2	8.5	Dose 4 24.5	10.8	p=0.09
			Dose 5 21.4	8.7	p=0.06
			Dose 6 18.3	11.8	NS

Discussion:
Drug interaction -
Cimetidine - The total body clearance of theophylline decrease from 57.6±21.8 ml/min before cimetidine to 39.5±9.5 ml/min. The mean half life of theophylline increase from 8.7 hours before cimetidine to 12 hours. From individual data, cimetidine significantly decreased the total body clearance in 8 out of 10 subjects. The apparent volume of distribution was unchanged.
Famotidine - From the data, famotidine does not seem to affect the pharmacokinetics of theophylline. The only parameters that change significantly was the volume of distribution. The renal clearance of theophylline decreased with time and was strongly correlated with urine flow rate in all individual. No change in overall renal clearances were observed during MK-208 and cimetidine administration.

Single dose/Multiple dose famotidine - From the data, there was no significant changes in the pharmacokinetics parameters considered. From the Cmin data, steady state appears to have been achieved by dose 1 on Day 4.

Conclusion:
1. Famotidine when given at 40mg bid (higher than recommended dosage range) does not seem to affect the disposition of theophylline.
2. Cimetidine at a dose of 300mg qid decrease the elimination of theophylline.
3. Pharmacokinetics of famotidine does not appreciably change after multiple oral dosing except for slight increase in Cmin and slight decrease in Tmax. No accumulation of the drug is expected in normal individuals with repeated doses.

Comments:
The above study is acceptable for the investigation of interaction of famotidine and theophylline. The firm could state in the labelling as regards to the lack of interaction of famotidine on theophylline. The above study also demonstrated that the pharmacokinetics of oral famotidine does not change on repeated dosing.

Reference 30 Zinny, M.A. #58 - Clinical Study Report.
An open-label, randomized three-way cross over study to assess the effect of MK-208, cimetidine and no drug treatment on the disposition of intravenous diazepam.

Objective:
To determine the effect of repeat oral doses of MK-208 and cimetidine on the pharmacokinetics of a single intravenous dose of diazepam.

Subjects:
13 volunteers mean age 29.8 (19-53) mean weight 165 (137-184) entered the study. 11 volunteers completed all three treatment. Volunteer 8 was removed due to prestudy liver function test, volunteer 13 (replacement) only completed 1 treatment. All subjects were judged to be in good health based on history, physical examination, routine laboratory tests and EKG.

Investigator/Site:
Miguel A. Zinny, M.D., David J. Greenblatt

Drug/Design:
Open randomized three-way cross over study.
Treatments
A MK-208 40mg bid - for 8 days
B Cimetidine 300mg qid - for 8 days
C No drug treatment - for 8 days.
Each study period lasted for 8 days. There was a minimum washout period of three weeks between study periods.
MK-208 Lot C-L405
Cimetidine Lot C-L406
Diazepam IV -investigator's supply.

Dosing/Sampling:
On day 2 of each study period, diazepam 10mg was given as a single IV infusion over 15 to 30 seconds at approximately 8am.
7 mls of blood was drawn at 0, 5, 15 and 30 minutes, and 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours.

Results:
Pharamcokinetic parameters for diazepam and desmethyldiazepam

Diazepam

Parameters	Treatment coadministration MK-208	Cimetidine	No Drugs	Power to detect 20% difference A or B vs C
Vl (l/kg)	0.21±0.06	0.24±0.05	0.26±0.14	0.29
Vd (l/kg)	1.08±0.36	1.16±0.37	1.17±0.38	0.87
T1/2 (hr)	52.6±25.5	72.2±31.8**	54.7±21.48	0.78
AUC (mg-hr/ml)	9.45±3.96	11.76±3.08**	9.78±4.11	0.88
Cl (ml/min/kg)	0.277±0.11	0.201±0.054**	0.276±0.138	0.65

Desmethyldiazepam

Parameters	Treatment coadministration MK-208	Cimetidine	No Drugs	Power to detect 20% difference A or B vs C
AUC (mg-hr/ml)	3.93±0.78	4.58±1.08*	3.84±0.79	0.85

* significantly different from diazepam treatment alone p 0.05
** significantly different from diazepam treatment alone p 0.05

Discussion:
By comparison of the plasma data obtained following diazepam treatment alone versus coadministration with cimetidine, cimetidine significantly prolonges the apparent elimination half-life, increased total area under the plasma concentration time curve, reduced total clearance and increased the AUC of desmethyldiazepam. No significant difference was observed in the volume of the central or the apparent volume of distribution of diazepam when cimetidine was coadministered.
MK-208 when coadministered with diazepam did not significantly change any of the above pharmacokinetic parameters.
The firm stated that plasma concentrations of MK-208 and cimetidine measured prior to and following diazepam administration were consistent with expected values for the selected dosing schedule.

Comments:
From the data, it could be seen that cimetidine affects the pharmacokinetics of IV diazepam, whereas famotidine has no effect. The firm also concluded that IV diazepam does not affect the pharmacokinetics of cimetidine nor famotidine. The firm could include this lack of effect of famotidine on IV diazepam in their labelling.

Reference 31 Williams, R.L. #55 - Clinical Study Report
An open-label, randomized two-way crossover study to assess the effect of MK-208 and cimetidine on the disposition of oral phenytoin and on hepatic blood flow.

Objective:
To examine the effect(s) of repeat doses of cimetidine and of MK-208 on:
1. The plasma kinetics of phenytoin given as a single oral dose.
2. The hepatic blood flow determined by kinetics of indocyanine green given intravenously.

Subjects:
10 subjects mean age of 30.6 years (20-47) weighing from 65.8-108.3lbs and in good health based on history, physical examination, routine laboratory tests and EKG participated.

Investigator/Site:
Roger L. Williams, M.D.

Drug/Design:
Open label, randomized two way crossover study.
Each study period was 13 days in duration and divided into 2 parts.
Part 1 - Baseline - Oral phenytoi 100mg and IV indocyanine green 0.5mg/kg was given on day 1 of the study. Blood and urine was collected for 96 hours to the morning of day 5.
Part 2 - 8 day drug treatment with either famotidine (40mg hs) or cimetidine (300mg qid) for seven days. Cimetidine was started in the morning on day 6 and famotidine at 9pm. Single doses of phenytoin 100mg po and intravenous indocyanine green 0.5mg/kg IV were given on the third day of this period (day 9). Blood and urine was collected for 96 hours to the morning of day 13.
Minimum of 14 day washout period.

Famotidine - Lot C-L878
Cimetidine - Lot C-L879
Indocyanine green and phenytoin was from the investigator's pharmacy.

Dosing/Sampling:
Subject fasted from midnight to 12 noon before the administration of phenytoin and indocyanine green. No xanthine containing food was allowed for 24 hours before and after administration of phenytoin.
Day 6 - Day 12. Famotidine 40mg was given at approximately 9pm each day. Cimetidine was given at 8am, 2pm, 7pm and 12 midnight. Each dose of medication was given with six ounces of water.
On Day 1 and 9, after the administration of phenytoin and indocyanine green, 5mls of blood was collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 15, and 20 minutes for the measurement of indocyanine green, and at 0, 1, 2, 4, 6, 8, 10, 24, 48, 72 and 96 hours after phenytoin administration.
At 0, 4 and 8 hours additional 10ml samples were drawn to determine protein binding during one baseline period on Day 1 and at the two treatment periods on Day 9.
On Day 1 and 9, after phenytoin adminstration, urine was collected at -1-0, 0-2, 2-4, 4-6, 6-12, 12-24, 24-48, 48-72, and 72-96 hours.

	Phenytoin				
	Treatment A		Treatment B		
	A1 Pre-MK-208	A2 MK-208	B1 Pre-Cimetidine	B2 Cimetidine	Overall p value
Cl (l/hr)	2.55±0.85	2.49±0.78	2.36±0.75	2.00±0.77	0.0061
KD (1/hr) (rate of constant elimination)	0.045±0.01	0.045±0.011	0.064±0.010	0.039±0.009	NS
V beta (l)	1020±485	1070±534	1150±512	1640±944	0.0004
Urine 0-96h (mg)	64.2±20.6	66.8±14.7	64.6±17.0	66.0±15.0	NS
	Indocyanine Green				
Plasma clearance (l/hr/kg)	0.734±0.258	0.860±0.411	0.678±0.190	0.915±0.219	NS
Blood clearance (l/hr/kg)	1.32±0.45	1.55±0.70	1.22±0.33	1.66±0.42	NS

Clearance and V beta means of A1, A2 and B1 are not significantly different. Clearance and V beta mean of B2 is significantly different from the others.

Conclusion:
The firm concluded the following:-
1. Treatment with MK-208 40mg hs for 7 days does not alter the biological disposition of phenytoin.
2. Their study confirms previous findings that cimetidine interferes with the biological disposition of phenytoin.
3. MK-208 may be administered concurrently with phenytoin.
4. MK-208 and cimetidine have no apparent effect on hepatic blood flow as determined by indocyanine green clearance.

Comments:
Though the firm have shown changes in the disposition of phenytoin when coadministered with cimetidine and no changes with MK-208, the lack of effect of MK-208 was only shown at one dose level (100mg of phenytoin). However, since MK-208 is not a highly metabolized drug, the possibility of competing or interference of liver metabolism of phenytoin is low.
The above study is acceptable in the investigating the effect of famotidine in the pharmacokinetics of phenytoin. The firm could incoporate their conclusions in their labelling.

Reference 32 Langman, M.J.S., #690 - Clinical Study Report
A study of the effect of famotidine (MK-208) on hepatic drug metabolism in healthy male volunteers.

Objective:
The objective of this study was to determine if famotidine, 40mg bid for seven days, prolongs the half-life of antipyrine or aminopyrine in healthy volunteers.

Subjects:
8 male subjects, mean age 23 y.o. (21-29) judged in good health by medical history, normal laboratory screen, physical examination and EKG.

Investigator/Site:
M.J.S. Langman

Drug/Design:
Open label study. Once during the week prior to start of famotidine treatment and on Day 7 following the morning dose of famotidine, each subject received 1 gm of antipyrine. Immediately following these oral doses of antipyrine, the subjects received 2 microcuries of C-14 aminopyrine as an intravenous bolus. Saliva and breath samples were obtained from each subject at specified intervals during pretreatment baseline and Day 7. Laboratory and physical examinations were performed prior to and after the administration of aminopyrine and antipyrine.

Famotidine - Lot GBC-K-626.
Antipyrine and C-14 aminopyrine provided by the investigator.

Dosing/Sampling:
Famotidine (40mg) were administered before breakfast and before the evening meals. Oral antipyrine followed by an intravenous bolus of C-14 aminopyrine was administered twice, once during the week prior to the first dose of famotidine and once following the last dose of famotidine. (Pre/post treatment).
Saliva samples were collected at 3, 6, 9, 12, 24, 30 and 36 hours following antipyrine.
Breath samples were collected at 15, 30, 45, 60 and 90 minutes and 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7 and 8 hours after adminstration of radiolabeled aminopyrine. Collection of each breath sample ceased when 2mmol of CO2 had been collected.

Analytical Methodology:
Saliva samples were assayed for antipyrine concentration as an index of plasma antipyrine concentration. C-14, CO2 dpm was measured via liquid scitillation counter to indicate the hepatic demethylation of aminopyrine.

Results:

Half lives of antipyrine and aminopyrine

Subject	Antipyrine			Aminopyrine		
	Baseline	Day 7	% Change	Baseline	Day 7	% Change
1						
2						
3						
4						
5						
6						
7						
8						
Median	12.6	11.2	-9.5	2.6	2.5	- 5.5

The percent changes from baseline to Day 7 were nearly all decreases for both antipyrine (median decrease of 9.5% , p=0.14) and aminopyrine (median decrease of 5.5%, p greater than 0.2) (Two-tailed Wilcoxon Rank-Sum Test).

The mean half-life of antipyrine was 13.1 hours at baseline and 11.8 hours on Day 7; the mean half-life for aminopyrine was repectively 2.9 and 2.7 hours. One of the subject had an increase in antipyrine half life and two of the eight subject had an increase in aminopyrine half life. The median percent change in half life at Day 7 of both substrates was a decrease of less than 10% from baseline level.
The firm cited a study (Miwa, G.T., Wang, R. and Argenbright, L., MSD Research Laboratories unpublished manuscript, 1984) - An in vitro study of spectral and kinetic characteristics confirmed a) cimetidine has a strong binding affinity with the ferrihaemoprotein of cytochrome p 450, an affinity not exhibited by famotidine or ranitidine, and b) cimetidine caused a concentration dependent inhibition of cytochrome p 450 substrate oxidative catabolism. Famotidine and ranitidine inhibits the substrates only at the highest of the four concentration tested (0.25, 0.5, 1.0, 2.0 mM). The results are shown below.

% Metabolism inhibition at 2.0 mM concentration.
(Pentobarbital-induced microsomes)

	O-Deethylase	N-Demethylase
Cimetidine	45%	34%
Ranitidine	25%	10%
Famotidine	10%	4%

In a similar experiment conducted by the investigator with cimetidine and ranitidine, cimetidine (1gm qd) all the subjects had an increased in half life of antipyrine (12.0±1.8 vs 15.8±2.8, p 0.05) and aminopyrine (3.7±0.4 vs 3.6±0.3, p 0.005). With ranitidine, two of six subjects had an increase in antipyrine half life and three of five subjects had an increase in aminopyrine half life.

Conclusion:
The firm concluded that their findings indicated that famotidine did not inhibit oxidative metabolism in the subjects evaluated and thus should not inhibit oxidative metabolism in clinical use.

Comments:
The above study is acceptable.

Reference 33 Ryan, J.R. #53 - Clinical Study Report
MK-208 and sodium warfarin in healthy volunteers.

Objective:
The objective of this study was to determine whether the anticoagulant effect of sodium warfarin therapy (as measured by prothrombin times) is affected by multiple doses of MK-208 in healthy male volunteers receiving subtherapeutic doses of sodium warfarin.

Subjects:
10 subjects, age 30.2±6.2 (20-40), weighing 157.2±18.2 (131-188), within ±20% of their height and weight and in good health by medical history, normal laboratory screen, physical examination and EKG.

Investigator/Site:
Jerome R. Ryan, M.D.

Drug/Design: (see attached table)
Open, multiple dose study.
Period I, subject received a single oral dose of sodium warfarin in the evening and prothrombin time was determined in the morining. The dose was adjusted by the investigator so that the subjects was subtherapeutically anticoagulated (Prothrombin time just a few seconds longer than the baseline, maximum of 1.5 times control). Steady state was defined as three prothrombin time determined on consecutive days within 15% of each other.
Period II, subjects received MK-208 40mg bid for 4.5 days, and their maintenence dose of sodium warfarin once a day for five days in the evening.
Period III, subjects received their maintenence dose of sodium warfarin once a day in the evening for 5 days followed by a brief washout period. During the washout period, the subjects receieved a single dose of 5mg Vitamin K. The washout lasted until the subjects prothrombin time was within one second of his baseline value.
Sodium Warfarin was supplied as 2, 2.5 and 5mg tablets (Lot - C-L336, C-L337, C-L338).
MK-208 40mg Lot C-L340
Vitamin K Lot C-L339

Dosing/Sampling: (See attached table for exact dose given)
Prothrombin times were determined on the morning of most study days prior to receiving drugs. Blood samples for MK-208 assay were collected just prior to and at 1, 2, 4, 8 and 12 hours following the first and last doses of MK-208.

Results:

Prothrombin time ratios by day of study

Treatment	Day	Mean	Median	Standard deviation	Min	Max
Warfarin only	7	1.288	1.301	0.092		
	8	1.256	1.276	0.094		
MK-208 and Warfarin						
	9	1.263	1.286	0.092		
	13	1.256	1.260	0.093		
Warfarin alone						
	15	1.232	1.232	0.097		
	17	1.199	1.206	0.103		
None						
	19	1.195	1.177	0.096		
	21	1.047	1.080	0.070		

Pairwise comparisons of posttreatmetn PT ratios with pretreatment and during treatment PT ratios

		Posttreatment day			
		warfarin		no warfarin	
	Day	15	17	19	21
Pretreatment warfarin	6	**	**	**	**
	7	**	**	**	**
	8	NS	*	*	**
During treatment MK 208 and warfarin	9	NS	*	*	**
	11	NS	*	*	**
	13	NS	*	*	**

* = p less than 0.05
** = p less than 0.01
NS = not significantly different

Mean plasma concentration of MK-208

		Hour postdose				
Dose	Predose	1	2	4	8	12
First	0	82.8	79.1	61.5	21.1	8.2
Last	16.5	69.5	82.2	65.1	23.2	11.9

Discussion:
The maintenence doses of sodium warfarin ranged from 2 to 10mg per day. The mean prothrombin time ratios observed from Days 6 to 8 remained at that level throughout period II (days 9 to 13) and then decreased from 1.23 to 1.05 on days 15 to 21.
There were no significant pairwise differences in PT ratios between days prior to MK-208 treatment (days 6 to 8) and days during MK-208 treatment (days 9 to 13) , but there were significant differences between days 6 to 13 and Days 15 to 21 for the pairs of days shown in the table on the previous page.
The MK-208 plasma level show compliance.

Conclusion:
The firm concluded the following:-
1. Repeated administration of MK-208 at 40mg q 12h for 4.5 days has no effect on the anticoagulant effect of sodium warfarin.
2. MK-208 is well tolerated when administered with sodium warfarin.

Comments:
The above study has demonstrated that at the doses given, MK-208 has no effect on the anticoagulant effect of sodium warfarin. The study is acceptable.

DISSOLUTION

The dissolution of famotidine tablets was conducted by the firm using the follwing:-

USP XXI apparatus II
900mls of pH 4.5, 0.1 phosphate buffer
Speed 50rpm

Choice of medium - The 0.1M phosphate, pH 4.5 buffer was selected for analysis purpose to control the UV spectral response which is pH dependent (See attached). A lambda maxima near 286nm in alkaline medium diminishes and one near 264 nm appears with increases in acidity. This 264 nm peak was reported to be stable at pH 4.5 and below. The firm further reported that while solution stability is best for near pH 7, it is more acceptable at pH 4.5 for this test. The solubility of famotidine at the lower pH is greater than 6 mg/ml versus 0.5 mg/ml at pH 7. However, both pH solubilities exceed the sink conditions required for the highest dose of 40mg.

Attached are the following:-
1. UV absorption spectrum in aqueous solution of famotidine at varying pH.
2. Table I - Profile dissolution of famotidine.
3. Table II - Comparative dissolution rates of famotidine crystalline forms.
4. Table III - Comparative dissolution rates of famotidine formulations (Merck versus Yamanouchi).
5. Famotidine tablets dissolution.

Comments:
1. The dissolution data demonstrates that famotidine tablets quickly solubilized at 15 minutes.
2. The firm should referenced the lot number of famotidine tablets used in their pivitol bioavailability and clinical study.
3. A suggested Q specification for famotidine tablets (20 and 40 mg) using the above method is Q =

The above study is acceptable.

Additional Dissolution Data - Pivotal bioavailability study lots

Additional dissolution for tablets used in the pivotal bioavailability studies and dose proportionality study (Dr. Zinny's Study No. 1, Dr. Williams Study No. 42, Dr. Ryan's Study No. 52) were requested by this reviewer from the firm and was submitted on April 3, 1986. The data are in the attached table.

Dr. Zinny's study No. 1

The lots (C-H348) used (Capsules, 5, 10, 20 & 40mg) had over 100% average dissolution in 30 minutes.

Lot #	Potency	Average Dissolution	Range
C-H348	5mg	102%	
"	10mg	105%	
"	20mg	104%	
"	40mg	108%	

Dr. Williams' Study No. 42

Lot #	Potency	Average Dissolution (30 minutes)	Range
C-K712	20mg caps	84%	
C-K713	20mg tablet	103%	
C-K714	40mg tablet	100%	

Dr. Ryan's Study No. 52

Lot #	Potency	Average Dissolution (30 minutes)	Range
C-L065	20mg tablet	105%	
C-L066	20mg tablet	85%	

Comments:
If the firm accepts the suggested Q= using the above dissolution method, both the pivotal 20 and 40mg tablets would pass. The Q value for famotidine 20 and 40mg tablets could be adjusted after more production batches dissolution data is submitted and the standard could then be established.

The firm is requested to send 3X100 each of the 20 and 40mg famotidine tablets to:-

Dr. V.K. Prasad,
Chief, Biopharmaceutics Laboratory Branch (HFN-224)
FOB-8,
200 C Street, S.W.
Washington, D.C. 20204

Labelling

The labelling for tablets, IV and suspension are acceptable except for the following need to be addressed.

1. From the AUC data in Study (Reference 20 - Dose proportionality), it was observed that famotidine is not dose proportional from 5 to 40mg orally, especially from 20-40mg. This lack of proportionality appears to be associated with the reported incomplete absorption of famotidine as the AUC increases disproportionally or decrease. However, from the IV data, famotidine was dose proportional in the range of 10 to 20mg given intravenously.

This lack of dose proportionality should be noted in the labelling.

2. The firm should include in the labelling suggested dose adjustment for renally impaired patient and appropriate equations to calculate creatinine clearance.

3. Since the presence of tubular secretion process is involved in the elimination of famotidine, the concommitant administration of other drugs that could interfere in this process should be administered with caution.

Assay Methodology

Instrument - HPLC - UV detector
Mobile Phase -
Column -
Extraction -

The methods were shown to be quantitative, reproducible, specific and had the required sensitivity for the concentration analysed.
Representative chromatograph are shown in Fig. 21-23. Sample calibration curve are shown in Fig. 19, 20.

Overall conclusion:
1. Linear kinetics was observed for famotidine in the range of [redacted] to [redacted] mg.
2. Urinary recovery of famotidine was 71% after IV administration and 28% after oral administration. Following oral administration of C-14 famotidine. 38% of the radioactivity was recovered in the urine and 51% recovered in the feces. The only known metabolite of famotidine is the S-oxide.
3. Half life of famotidine:-
   Healthy young subjects (IV or PO) - 2.8 hours.
   Healthy elderly (IV or PO) - 4.0 hours.
   Renally imparied - increasing $T_{1/2}$ and may exceed 20 hours in anuric patients.
4. Plasma/Renal clearance:-
   Large intersubject variablility was observed.
   Healthy young subjects - 424ml/min, 316ml/min.
   Healthy elderly - 240ml/min, 190ml/min
   Renally imparied - plasma and renal clearance decreases with increasing renal dysfunction.
   The value from renal clearance suggest tne presence of a tubular secretion process.
5. Bioavailability of oral famotidine tablet average 42-45% and was slightly increase with food and slightly decrease with antacid. The firm concluded that this effect was small and probably are not clinically significant.
Bioavailability of oral famotidine tablet was similar in the young and older population.
6. Plasma protein binding of famotidine was shown to be approximately 16% and was shown to be concentration independent in the therapeutic concentration range.
7. Famotidine exist in two polymorphic forms. From studies using capsule dosage forms, this polymorphism does not affect bioavailability. Dissolution profiles from tablets made of the two forms were similar.
8. From drug interaction studies, famotidine does not appear to affect the pharmacokinetic profile of aminopyrine, antipyrine, diazepam, theophylline, indocyanine green and phenytoin in the dosage strength examined in each study. Famotidine does not appears to potentiate the anticoagulant effect of warfarin in the dose studied. From in vitro studies, famotidine showed low affinity for hepatic microsomal cytochrome P-450 enzyme systems.

Conclusion:
Studies - acceptable, Application - acceptable.

The Division of Biopharmaceutics have reviewed NDA-19-462, Famotidine tablets 20, 40mg (Submission Dates:- 6/24/85, 8/9/85, 4/3/86). The data submitted by the firm has satisfied the requirements and the Division of Biopharmaceutics recommends the approval of NDA 19-462, Famotidine tablets 20, 40mg.
The comments in the labelling section should be forwarded to the firm. (See comments on labelling on p.37).

The firm is requested to send 3X100 each of the 20 and 40mg famotidine tablets to:-

Dr. V.K. Prasad,
Chief, Biopharmaceutics Laboratory Branch (HFN-224)
FOB-8,
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cc: NDA 19-462(orig.), HFN-110(2), HFN-226(Lam), HFN-344, Chron, Drug and FOI files.

SYL:syl:4-2-86

Tables & Figures.

Table 1

Composition (mg) of PEPCID Tablets

Component	20-mg Film-Coated Tablet	40-mg Film-Coated Tablet
Famotidine	20.0	40.0
Film Coating		

Table 2

Typical Physiochemical Properties of PEPCID Tablets[a]

		20 mg Tablet	40 mg Tablet
Lot #		0208-FCT-010-B002	0208-FCT-012-E002
Label Claim		20 mg	40 mg
Assay Value		19.8 mg	40.3 mg
Dissolution Time, 30 min		103%	100%
Content Uniformity	Mean Range	19.9 mg	40.8 mg
Thickness	Mean Range	4.23 mm	4.09 mm
Hardness	Mean Range	12.0 kg	14.6 kg
Uncoated Weight	Mean Range	202.0 mg	201.0 mg
Coated Weight	Mean Range	211.0 mg	206.8 mg
Disintegrated Time	Mean	2.7-3.5 min	1.7-2.9 min
Moisture		2.3%	2.6%

[a] The 20 mg tablet is represented by lot 0208-FCT-010-B002, the 40 mg tablet is represented by lot 0208-FCT-012-E002; both were used in the PEPCID tablet bioavailability study (M.A. #42; Ref. 12).

Table 3

Plasma Levels and Urinary Recoveries (Mean ± S.D.) of Famotidine Following Intravenous Administration of 20 mg in Sixteen Young Healthy Subjects (Ref. 12)

Plasma		Urinary Recovery	
Time (hr)	Cp, ng/ml	Time Interval (hr)	mg
0.083	475.1 ± 220.0	0-2	8.96 ± 2.84
0.167	410.6 ± 195.6	2-4	2.69 ± 1.29
0.333	272.0 ± 46.0	4-6	1.08 ± 0.78
0.667	214.3 ± 98.0	6-8	0.64 ± 0.31
1	163.4 ± 49.0	8-12	0.64 ± 0.19
1.5	141.5 ± 106.0	12-24	0.58 ± 0.46
2	98.5 ± 23.7	24-36	0.04 ± 0.13
2.5	87.3 ± 31.4	36-48	0
3	84.. ± 21 °	48-72	0
4	64.2 ± 21.5		
6	41.6 ± 19.7		
8	25.4 ± 10.9		
10	19.8 ± 10.2		
12	11.2 ± 9.0		
24	0		
36	0		

Table 4

Summary of Pharmacokinetic Parameters (Mean ± S.D.) of Famotidine Following Single Intravenous Dose of 20 mg in Sixteen Healthy Subjects (Ref. 12)[a]

Plasma Clearance, ml/min	463 ± 160
Rena Clearance, ml/min	310 ± 120
Non-Renal Clearance, ml/min	15[illegible] ± 78 [b]
Half-Life, hours	2.83 ± 0.99
Urinary Recovery, % of dose	66.8 ± 14.9

[a] Values in parenthesis indicate range.

[b] Difference between plasma clearance and renal clearance.

Table 5

Plasma Levels and Urinary Recoveries of Famotidine on Day 1 and Day 8 (Mean ± S.D.) of Six Subjects Following Repeated Administration (20 mg b.i.d. at 8:00 am and 5:00 pm for 15 Doses) of i.v. Famotidine (Ref. 15)

Day	Time, hr	Plasma Level ng/ml	Day	Time, (hr)	% of Dose Recovery in Urine
1	0	0	1	0-2	55.70 ± 8.90
	0.17	368.19 ± 68.07		2-4	13.10 ± 1.60
	0.33	221.37 ± 53.05		4-6	7.00 ± 0.95
	0.5	175.41 ± 53.00		6-9	4.60 ± 1.30
	1	126.69 ± 32.20		9-24	79.20 ± 7.85
	2	96.34 ± 19.02			
	4	63.25 ± 13.89	8	0-2	64.10 ± 7.75
	6	31.17 ± 10.47		2-4	15.40 ± 3.30
	9	14.34 ± 12.87		4-6	6.35 ± 2.80
				6-9	6.90 ± 4.35
3	0	5.83 ± 5.56		9-24	5.85 ± 1.55
	9	16.43 ± 16.88			
6	0	6.44 ± 6.14			
	9	16.21 ± 16.76			
8	0	5.43 ± 5.80			
	0.17	388.12 ± 148.71			
	0.33	266.61 ± 35.30			
	0.5	207.89 ± 82.72			
	1	180.20 ± 55.66			
	2	128.00 ± 40.82			
	4	69.17 ± 28.01			
	6	35.26 ± 14.45			
	9	18.19 ± 11.34			

Table 6

Summary of Pharmacokinetic Parameters (Geometric Mean)
of Famotidine Following Repeat Intravenous
Administration (20 mg b.i.d. at 8:00 am and 5:00 pm for 15 Doses)
in Six Healthy Subjects (Ref. 15)[a]

Plasma Clearance, ml/min	313
Renal Clearance, ml/min	259
Non-Renal Clearance, ml/min	54 [b]
Half-Life, hours	2.7
Urinary Recovery, % of Dose	82.9

[a] Values in parenthesis indicate range.

[b] Difference between plasma clearance and renal clearance.

Table 7

Plasma Levels and Urinary Recovery (Mean ± S.D.) of Famotidine Following 20 mg Intravenous Administration in Eight Healthy Elderly Subjects (Ref. 16)

Time (hr)	Plasma Concentration, ng/ml	Time (hr)	Urinary Recovery mg
0.083	757.9 ± 210.2	0-2	2.35 ± 1.53
0.166	579.5 ± 124.7	2-4	2.86 ± 0.88
0.333	363.2 ± 91.0	4-6	2.39 ± 0.91
0.667	274.9 ± 86.4	6-9	2.92 ± 1.26
1	205.4 ± 46.3	9-12	1.50 ± 0.57
2	157.7 ± 29.8		
3	132.0 ± 44.1		
4	98.0 ± 20.9		
6	66.2 ± 12.9		
9	42.7 ± 12.9		
12	26.8 ± 9.6		

Table 8

Summary of Pharmacokinetic Parameters (Geometric Mean) of Famotidine in Elderly Subjects Following a Single Dose of 20 mg i.v. (Ref. 16)[a]

Plasma Clearance, ml/min	233	
Renal Clearance, ml/min	183	
Non-Renal Clearance, ml/min	54	[b]
Half-Life, hours	3.95	
Total Urinary Recovery, % of Dose	77.3 (	[c])

[a] Values in parenthesis indicate range.

[b] Difference between plasma clearance and renal clearance.

[c] Subject showing a -33 ml/min for non-renal clearance had a urinary excretion (110.9%) exceeding administered dose.

Table 9

Individual Pharmacokinetic Parameters Obtained in Study M.A. #404 (Ref. 17) in 18 Patients with Renal Insufficiency (in Descending Order of Creatinine Clearance). Patients Received 10 mg Famotidine by i.v. Bolus

Subject	Creatinine Clearance, ml/min	Urinary Recovery, % of Dose	Plasma Clearance, ml/min	Renal Clearance, ml/min	Non-Renal Clearance, ml/min	Half-Life, hours
20						
3						
1						
19						
14						
18						
2						
10						
17						
5						
11						
4						
7[a]						
8[a]						
9[a]						
12[a]						
13[a]						
16[a]						

[a] Patients 7, 8, 9, 12, 13, and 16 are anuric; no urine output.

Table 10

Individual Creatinine Clearance and Famotidine Plasma Half-Life Reported in Study M.A. #42 (16 Healthy Subjects; Ref. 12) and M.A. #518 (Eight Elderly Subjects; Ref. 16)

		Famotidine Pharmacokinetic Parameters					
Subj.	Creatine CL ml/min	Renal CL ml/min	Half-Life, hours	Plasma CL ml/min	Non-Renal CL ml/min	Urinary Recovery, % of Dose	Ref.
1							12[a]
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
1							16[b]
2							
3							
4[c]							
5							
6							
7							
8							

[a] Values are from i.v. treatment period.
[b] Creatinine clearance adjusted to 1.73 m^2
[c] Subject 4 showed negative non-renal clearance for famotidine, excluded in Figures 5-8.

Table 11

Summary of Yamanouchi Renal Insufficiency Study
(Ref. 18)[a]

Group	Creatinine Clearance, ml/min	Half-Life hours	Plasma Clearance, L/hour	Renal Clearance, L/hour
I	98.9	2.6	22.7	16.6
II	73.8	3.0	21.4	14.7
III	49.2	4.5	13.7	8.9
IV	10.3	11.7	4.5	1.0
V	0	13.7	6.3	--
V[b]	4.9	13.0	4.3	0.6

[a] All values are group mean values.
[b] These are Group V patients under dialysis.

Table 12

Plasma Level of Total Radioactivity and Famotidine (Mean ± S.D.)
Following Oral Administration of 20 mg
(Containing 20 μCi ^{14}C-Famotidine) to Four Healthy Subjects
(Ref. 19)

Time (hr)	Famotidine ng/ml	Total Radioactivity ng-eq/ml
0	0	0
0.33	20 ± 2	19 ± 15
0.67	33 ± 16	42 ± 19
1	53 ± 30	60 ± 24
1.5	59 ± 17	58 ± 19
2	56 ± 30	58 ± 20
3	56 ± 23	54 ± 22
4	49 ± 22	49 ± 21
5	38 ± 16	45 ± 18
6	26 ± 13	35 ± 12
8	18 ± 10	22 ± 8
10	10 ± 3	21 ± 10
12	4 ± 4	11 ± 4
24	0	4 ± 1

TRADE NAME: PEPCID (FAMOTIDINE) TABS
GENERIC NAME: FAMOTIDINE

Summary Basis of Approval
Cover Form

Appl #. 019462 Firm: MS AND D RES LABS
Reviewing Div: 180
Trade Name: PEPCID (FAMOTIDINE) TABS
Generic Name:
FAMOTIDINE

Approval Letter: Y	Statistician Review: Y
SBA Form: N	Bio/Dissolution Review: Y
Final Printed Labeling: Y	Microbiologist Review: N
Medical Officer Review: Y	NAS/NRC Review: N
Chemist Review: Y	Pharmacologist Review: Y
Federal Register Notice: N	Completion Date: 02-APR-92

STATISTICAL

REVIEW

Statistical Review and Evaluation

NDA #: 19-462/Drug Class: 1C

Applicant: Merck, Sharp & Dohme Research Laboratories

Name of Drug: PEPCID (Famotidine) 40 mg/hs

Indication: For treatment of active duodenal ulcers, gastric ulcers, the prophylactic use in duodenal ulcer disease, and the treatment of pathological hypersecretory conditions such as Zollinger-Ellison Syndrome

Documents Reviewed: Volumes 1.1 and 1.39-1.46 of the NDA submission dated June 24, 1985.

The statistical section of this NDA submitted to the Division of Biometrics contains one domestic (placebo control) and one international (ranitidine control) duodenal ulcer study each of which covers an acute phase followed by a six-month maintenance phase. It also contains an international (placebo control) and a Japanese (gefarnate control) acute gastric ulcer trial. This review will mainly discuss the efficacy results of these trials. The safety aspects of these studies have been covered in detail by Dr. Bachrach/HFN-110, the medical reviewer, and will not be discussed in this review.

Since similar designs and methods of analysis were used in all four studies, they will be described in detail only in the first study.

Domestic Duodenal Ulcer Study

The principal objectives of this study were to determine the clinical efficacy and safety of doses of famotidine in the short-term treatment of active duodenal ulcers and in the long-term maintenance treatment of duodenal ulcer disease.

The acute phase of this study was a multiclinic (34 investigators), double-blind, randomized, placebo-controlled trial lasting 8 weeks. During the initial screening visit (baseline), a complete physical and laboratory examination were performed and pertinent baseline information (e.g., alcohol, smoking, etc.) were obtained. An endoscopy was performed at this time to verify the presence of a duodenal ulcer and to determine the number, size and location of the ulcer(s). The presence of duodenitis or erosions was also noted. The patients selected had a primary diagnosis of active duodenal ulcer confirmed by endoscopy. Patients with a 0.5 to 2.5 cm lesion within the duodenal bulb or pyloric channel who exhibited clinical symptoms of active duodenal ulcer and met admission criteria were permitted to enter the acute phase of the study. Patients were randomized to either famotidine 40 mg/hs, 20 mg/bid, 40 mg/bid or placebo. Clinical symptoms were assessed and endoscopies were performed at Weeks 2, 4 and 8 to verify the healing status of the duodenal ulcer. Ulcers were considered to be healed if no ulcer was present (defined as complete epithelialization of the ulcer). Ulcers with

partial/incomplete epithelialization were considered as not healed. Patients were asked to record daily the occurrences of night and day pains, the number of antacid tablets and the number of doses of the prescribed treatment medication taken. Pains were recorded on the following scale: 0=none, 1=mild, 2=moderate and 3=severe. Patient's daily pain scores for Days 1 to 7 and weekly pain evaluation for Weeks 2 to 8 were recorded by the investigator on the CRF. Adverse clinical experiences reported were volunteered by the patient and were not solicited by the clinicians.

If a patient's ulcer was healed within the 8-week treatment period as verified by endoscopy during one of the three visits, then he was withdrawn from the acute phase and became eligible for re-randomization into the 6-month maintenace phase of the study. Patients whose ulcers had not healed at the end of 8 weeks of therapy were considered as treatment failures and were not considered eligible for the maintenance study. For patients who entered the maintenance phase of the study, endoscopies were done to verify the presence or absence of duodenal ulcers at 3 and 6 months or at any time at the discretion of the clinician when the patient reported symptoms suggestive of the presence of an ulcer. During endoscopy, the presence of duodenitis or erosion was noted by the endoscopists. Adverse clinical experiences reported were volunteered by the patients and were not solicited by the clinician. It appears that pain and symptom data were not systematically collected during this maintenance period. This was not discussed in the statistical section and no pain and symptom data were provided.

Sponsor's Study Results

Acute Phase

A total of 384 patients entered the acute phase and were randomized to the four treatment groups. These treatment groups were generally comparable at baseline with respect to various pertinent patient characteristics such as smoking, ulcer size etc. (see Table 1). During this acute phase, 21 patients were either off drug or violated protocol. Of the remaining 363 patients, 10 had no treatment data and 59 were discontinued due to adverse experience, ineffective therapy or other reasons. There were significantly more placebo patients than famotidine patients among the therapeutic failures in each of the treatment groups.

Efficacy analyses were done on two data sets: the "per protocol" and the "all patients treated" data sets. The former excluded all patients who were either off drug or protocol violators, and the latter included all patients who had baseline and some post-baseline treatment values.

The primary efficacy parameter was the cumulative frequencies of healed ulcers observed via endoscopy at Weeks 2, 4 and 8. Crude healing rates were compared among treatment groups using Fisher's Exact test (see Table 2). In this analysis, dropouts were considered as not healed. The Kaplan-Meier product limit (life-table) estimates of the healing rates were also obtained. This method assumed that dropouts healed at the same rate as those observed for patients who completed the study (see Table 2). Since these results were very similar for the two data sets, only the results based on the "per protocol"

data set are presented here in lable 2. As noted earlier, because the placebo group had significantly more dropouts than the treatment groups, the crude healing rates comparison would tend to be more favorable to famotidine. Therefore, in this case, the Kaplan-Meier product limit estimates would be more preferrable. However, by either methods, the famotidine treated groups all had significantly higher cumulative healing rates than the placebo group at all time points (for example 88%-89% for famotidine vs. 55% for placebo at 8 weeks $p < 0.01$). The relationship between the various concomitant factors and ulcer healing were also assessed. The results from this trial suggested that initial ulcer size, ulcer history, drinking and esophagus condition may significantly affect ulcer healing (See Table 3). Further analysis indicated that the observed differences in healing rates between the famotidine groups and the placebo group were maintained after adjusting for these factors. However, it would be of interest to point out that for this study the observed treatment differences in healing rates were higher among non-drinkers than among drinkers (placebo drinkers appeared to heal better than placebo non-drinkers) and higher among patients with normal esophagus condition than among patients with abnormal esophagus condition (placebo patients with abnormal esophagus condtion appeared to heal better than placebo patients with normal esophagus condition).

Secondary efficacy measures included reduction from baseline in day pain, night pain and antacid consumption. Day and night pains were assessed by median time until pain relief (and no reoccurrence) using the Mantel-Haenszel method stratifying for baseline pain score. The results for the "per protocol" data as shown in Table 4 suggested that the famotidine patients experienced significantly greater pain relief than the placebo patients beginning Day 1 ($p < 0.001$) both in terms of proportion of patients with pain relief and median time until pain relief. Similar results were observed based on the "all patients treated" data. Antacid consumption was evaluated by comparing the proportion of patients in each group who took antacid therapy at Days 1, 2-7 and Weeks 2, 4 and 8 and at any time during the study and by comparing the mean numbers of antacid therapy during Weeks 1, 2, 4, and 8. The results based on "per protocol" data are displayed in Table 5. Generally, antacid usage was significantly less ($p < 0.01$) in the famotidine groups than in the placebo group.

Reviewer's Comments

1. In order to check the internal consistency of the observed treatment differences in healing rates across investigators, centers with fewer than 15 patients were combined into a single pool (accounting for 40% of total). With the exception of a few investigators (mainly due to small sample sizes within treatment groups), the treatment differences remained generally consistent across these investigators; no significant treatment by investigators interaction was detected.

2. The healing data was also analyzed by this reviewer using the Mantel-Haenszel method and the result corroborated the sponsor's finding.

3. The pain data for this study suggested that famotidine provides fast pain relief (starting with Day 1) to duodenal ulcer patients with baseline

pain. The median time to pain relief was significantly shorter among famotidine patients than among placebo patients at all levels of pain severity.

Maintenance Phase

Of the 280 patients (based on "all patients treated" data set) who had a healed ulcer during the acute phase of this study, only 177 patients (from 27 investigators) who had an ulcer healed within the 8 weeks period were re-randomized into three treatment groups (famotidine 40 mg/hs, 20 mg/hs and placebo) during the maintenance phase. These treatment groups were dissimilar at the baseline with respect to age, age at first ulcer, the week in the acute phase when the ulcer was healed, the number of ulcers, duration of ulcer disease, and condition of the stomach (see Table 6).

Ulcer relapse rate was assessed using the Mantel-Haenszel method based on the "per protocol", "all patients treated" and "dropout-included" approaches. Various definitions of the time of relapse, dropout and study completion were used. All these analyses provided essentially the same results. In this review, only the relapse rate analysis using the Mantel-Haenszel method based on the "per protocol" data set will be discussed. The results of the analysis as shown in Table 7 was carried out over the following time points: period 1 (day 1-42), period 2 (day 43-105) and period 3 (day 106 and later). It suggested that the famotidine treated groups had significantly fewer relapses within all three periods (except for period 3 between famotidine 40 mg/hs and placebo) than the placebo group. Moreover, the cumulative relapse rates based on the Mantel-Haenszel method for the famotidine groups were significantly ($p < 0.01$) lower than that for the placebo group at all time points and after 6 months (respectively 30.2%, 26.2% and 69.9%, $p < 0.01$). To account for baseline differences in some concomitant factors and to adjust for factors that were found in this study to have significant relationship to ulcer relapse, statistical models including terms for treatment, concomitant factors, and treatment by concomitant factor interaction were used. In all cases, the significant differences in ulcer relapse rates between the famotidine treated groups and the placebo group were maintained.

Reviewer's Comments

1. Even though patient visits were scheduled at weeks 4, 12 and 24, endoscopies were performed only at weeks 12 and 24 or at any time at the investigator's discretion if symptoms suggested the presence of ulcer. Therefore, the sponsor's choice of the 3 periods may be misleading in the sense that the first period does not correspond to an endoscopy time. Ulcers that were detected during period 1 were most likely to be all symptomatic; however, because of the width of the relative day range, some symptomatic relapses may be included in the second period. In any event, the absence of pain and symptom data did not permit differentiation between scheduled and unscheduled recurrences.

2. Since only data available by the cutoff date of January 7, 1985 were used in the maintenance phase of this study, estimates of relapse rates may be biased in favor of famotidine, because placebo patients with symptomatic

and/or earlier relapses would be more likely to have data available by the cutoff date. For this study, this bias may affect the observed recurrence rates for all three periods, because about 25% of the patients had enrolled for less than 6 months and only about 22% had either completed or had the opportunity of completeing the 12-month study. More detailed information, which may not be available for this study, would be required to assess the magnitude and effect of this bias.

3. Since only patients whose ulcers were healed within 8 weeks during the acute phase of this study were entered into the maintenance phase, these were very selective patients. They tended to be mostly famotidine responsive patients and to have faster healing time. In fact, the sponsor's data indicated that about 80% of these patients were healed on famotidine in the acute trial; moreover, about 85% of these patients had their ulcers healed within 4 weeks.

4. See overall summary at the end for further comments with regard to the design issue.

International Duodenal Ulcer Study

The objective of this study was to compare the clinical efficacy and safety of 3 doses (same as in the preceeding acute study) of famotidine to 150 mg/bid dose of ranitidine in the short-term treatment of acute duodenal ulcers and to determine the clinical efficacy and safety of 20 mg/hs of famotidine in the long-term maintenance treatment of duodenal ulcer disease. The study design was similar to the preceding domestic duodenal ulcer study except with ranitidine in place of placebo in the acute phase. Some pain and symptom data were available in the 6-month maintenance phase of this study. The approach and the methods of analysis were generally the same as those employed in the preceding study.

Sixty-eight investigators from nineteen countries enrolled a total 1031 patients in the 8 weeks acute phase of the study. Of these, 939 had their ulcers healed during the acute phase and only 645 were enrolled into the maintenance phase. The results of this study is discussed below.

Sponsor's Study Results

Acute Phase

During the acute phase of this study, 1031 patients were randomized into four treatment groups: famotidine 40 mg/hs, 20 mg/bid, 40 mg/bid and ranitidine 150 mg/bid. These treatment groups were generally similar with respect to various baseline characteristics (e.g., smoking, drinking, etc.) except for a slight under representation of females in the latter two groups. There were 51 protocol violators and 46 dropouts who were distributed evenly among the treatment groups. The protocol violators were excluded from the "per protocol" efficacy analysis. The crude rates and the Kaplan-Meier estimate of the cumulative healing rates are shown in table 8. The crude healing rates demonstrated that famotidine 40 mg/bid was significantly superior to famotidine 40 mg/hs at Weeks 2 and 4, famotidine at 20 mg/bid was

significantly superior to famotidine 40 mg/hs at Week 4. However, no significant differences were demonstrated among the treatment groups at Week 8. At the end of the study, both 40 mg/bid and 20 mg/bid were significantly better than 40 mg/hs.

Overall, the results suggested that famotidine at 40 mg/bid was significantly more effective than famotidine at 40 mg/hs early on; but this superiority was not maintained by Week 8. The same result may be observed of famotidine 20 mg/bid and ranitidine 150 mg/bid relative to famotidine 40 mg/hs. However, their numerical superiority over the latter (40 mg/hs) did not achieve statistical significance. The difference between famotidine 40 mg/bid and 40 mg/hs remained consistent across various levels of factors such as initial ulcer size, smoking, drinking, number of ulcers and baseline day/night pain which suggested an association with ulcer healing rates These observed differences were not evident within individual investigator or within each country. Indeed within individual investigators with at least 28 patients (only 6 such investigators), no consistent differences between famotidine 40 mg/bid and 40 mg/hs were observed; a significant difference was observed only in the pooled data set consisting of investigators each with fewer than 28 patients. Within the two countries with the most number of patients (German, N=209 and Italy, N=245), there were no significant differences among the treatment groups.

With respect to day/night pain relief and antacid use, all treatment groups reported significant pain reduction from baseline and there were generally no significant difference between treatment groups (see Table 9) except for a significantly longer median time to night pain relief and a significantly greater proportion of patients with antacid usage during the first week observed in the ranitidine group (see Table 10).

Reviewer's Comments

The acute phase of this study was an active (ranitidine)-controlled trial. Therefore, questions concerning whether the observed outcome would have differed significantly from the outcome of a placebo group had one been present and whether the absence of a placebo control would result in a "positive bias" naturally arise. However, from available controlled trial results from the published literature, the sponsor provided reasonable arguments which suggested that famotidine would likely be superior to placebo had one been present (see Vol. 1.47, section L: Special Report).

Maintenance Phase

Of the 939 patients who completed the acute phase of the trial with an endoscopically verified completely healed duodenal ulcer, 645 were re-randomized to either famotidine 20 mg/hs or placebo in the maintenance phase. Assessment of clinical symptoms were made at weeks 0, 4, 12 and 24 with endoscopies performed at weeks 0, 12 and 24. Endoscopy may be performed at the discretion of the investigator at an unscheduled visit when a patient reported symptoms suggestive of ulcer recurrence. The two treatment groups were generally similar with respect to various baseline characteristics except for smoking; the placebo group had slightly more smoking patients (p=0.074).

Duodenal ulcer relapse rate was analyzed the same way as was done in the preceding domestic study. The crude rates and the life table rates (Kaplan-Meier) for the three periods are shown in Table 11. Famotidine 20 mg/hs group had significantly lower relapse rates than the placebo group for all three periods (30% vs 73%, for the 3rd period, $p < 0.01$)

Factors found to be related to duodenal ulcer relapse in this study included smoking, ulcer history, duration of ulcer, onset age, other conditions in the duodenum, week healed in the acute study and antacid use. However, no significant treatment by factor interaction was found. Treatment differences were also found to be consistent across investigators.

Table 12 provides the distribution of day and night pain at baseline and at the end of the study for the two treatment groups (refer also to Medical Reviewer's Table 4b). At baseline, 80-90% of the patients had no pain. This reflects the fact that these patients' ulcers had just completely healed at baseline. However, at the end of the study, the proportion of patients with pain (day/night) in the placebo group was significantly greater ($p < 0.01$) than that observed in the famotidine group.

Overall, the proportion of patients who took antacid therapy at any time during the study was significantly higher in the placebo than in the famotidine group (49% vs 33%, $p < 0.01$).

Reviewer's Comments

1. Among those patients who withdrew from the trial, there were more placebo patients (26 vs 7) who dropped out on account of therapy ineffectiveness (exactly what does this mean in a maintenance trial?) and more famotidine patients (41 vs 22) who were lost to follow-up/other reasons. When these patients were assigned the same recurrence rates as observed for the respective treatment groups, similar results were obtained.

2. As in the domestic maintenance trial, the patients enrolled in this maintenance trial were also mostly famotidine responsive patients (75% of these patients were treated by famotidine in the acute phase) and 80% of them had their ulcers healed within 4 weeks during the acute phase.

3. Even though 68% of these patients were enrolled prior to 1984, the bias (see reviewer's comment (2) on the domestic maintenance study) favoring famotidine due to the cutoff date of December 27, 1984 would affect the 3rd period relapse rates in this study.

4. The availability of pain and symptom data in this study ought to provide some useful information concerning scheduled and unscheduled relapse rates and estimate of the bias discussed in Comment (3). However, these data were not readily available in the submission.

International Gastric Ulcer Study

The primary objective of this study was to determine the efficacy and safety of famotidine 40 mg/hs in the short-term treatment of acute gastric ulcer. This was an 8-week double-blind, randomized, multicenter (44 investigators across 14 countries) and placebo-controlled study. Patients with a primary diagnosis of active gastric ulcer between 0.5 and 2.5 cm confirmed by endoscopy were eligible to enter the study subject to some other entry criteria. Assessment of clinical symptoms and endoscopies were performed at weeks 0, 4, 6 and 8. Patients whose ulcers had completely healed by the time of any visit were considered to have completed the study. Patients were instructed to record daily pain occurrences and antacid consumption. Concomitant therapies, antacid consumption and dosage of test drug taken during the study were recorded by the investigator at each visit.

Sponsor's Study Results

A total of 336 patients entered the study. One hundred sixty-seven patients were assigned the famotidine 40 mg/hs treatment and 169 the placebo treatment. Both treatment groups were comparable at baseline with respect to various pertinent baseline characteristics except for drinking habit which was more prevalent among the placebo patients than among the famotidine patients (59% vs 44%, $p < 0.01$).

Both the crude cumulative healing rates and the Kaplan-Meier life-table estimates of the healing rates were significantly ($p < 0.01$) greater for the famotidine group than for the placebo group at weeks 4, 6 and 8 (for example, at 8 weeks, 80% for famotidine 40 mg/hs vs. 54% for placebo, $p < 0.01$, see table 13).

The data suggested significant relationship between ulcer healing and initial ulcer size and antacid use. However, no significant treatment by factor and treatment by investigator interactions were found; the treatment differences were generally consistent across investigators and various factor.

The two treatment groups were similar at baseline with respect to day pain with over 73% of patients having moderate or severe pain. Patients from both treatment groups experienced significant pain relief starting at day 1 ($p < 0.01$) and continue to the end of the study. However, the difference in the proportion of patients with pain relief at any time during the study was only marginally different between treatments ($p=0.06$). However, the famotidine group had a significantly shorter median time to pain relief (14 days vs 35 days, $p < 0.01$). No significant treatment difference was observed in the relief of night pain. There were significant differences ($p < 0.05$) between the treatment groups during the first week in the proportion of patients taking antacid therapy and in the overall mean number of days of antacid therapy (famotidine group was shorter by only a day).

Reviewer's Comments

The method of analysis for this study appeared to be appropriate. Famotidine was superior to placebo at the end of 8 weeks based on both the crude rates

and the Kaplan-Meier life-table estimates. Because of the significantly greater proportion of placebo therapeutic failures ($p < 0.01$), the Kaplan-Meier estimates were more preferrable. However, based on these estimates, the superiority of famotidine over placebo was also significant at weeks 4, 6 and 8 ($p < 0.01$).

Japanese Gastric Ulcer Study (Yamanouchi)

This was an 8-week, multicenter (32), double-blind, randomized, gefarnate-controlled study conducted according to Yamanouchi Pharmaceutical Co.'s protocol. The study compared the efficacy and safety of famotidine 20 mg/bid to that of gefarnate 100 mg/tid in patients with endoscopically confirmed single gastric ulcer of circular or oval shape with at least 0.5 cm in major axis at stage A_1 or A_2 of Sakita and Miwa's 6-stage classification (see Table 14). One hundred ninety-two patients were entered and assigned at random to either famotidine 20 mg/bid or gefarnate 100 mg/tid. Clinical visits were scheduled at weeks 4 and 8. Endoscopies were performed at these visits.

The primary efficacy measure was the cumulative frequencies of endoscopically confirmed ulcer healing as defined by stage S_1 or S_2 of Sakita and Miwa's classification (see Table 14) at each time points (week 4, week 8 and after week 8). A supporting measure was ulcer related pains which were divided into pain after meals, pain in a fasting state, night pain and pain unrelated to meals. Pain was rated by the patients as to its degree: none, mild, moderate and severe.

The crude healing rates and the Kaplan-Meier estimates are displayed in Table 15. The famotidine 20 mg/bid group had significantly ($p < 0.01$) greater healing rates than gefarnate 100 mg/tid group at all time points. The observed treatment difference was generally consistent across various factor levels. Data did not permit the examination of treatment by investigators interaction.

Surprisingly, a large number of patients (40%-70%) had no pain at baseline. The proportion of patients with pain relief during the study was not significantly different between the two treatment groups. However, among patients with moderate and severe pains at baseline, the famotidine group appeared to have shorter median time to pain relief.

Reviewer's Comments

If the control, gefarnate, is equivalent to placebo, then the result of this study would provide evidence in support of the efficacy claim for famotidine. However, no information was provided in the submission to substantiate this assertion. It is not sufficient simply for the sponsor to consider them to be equivalent. Does there exist information (well-conducted trials in Japan or elsewhere) that convincingly demonstrated their equivalence? (Gefarnate is a marketed drug in Japan, among other countries, but not in the United States.) If not, then on account of the relatively low observed gefarnate healing rate of 24% at week 8 when compared to an 8-week placebo healing rate of 54% in the preceeding trial and a 6-week healing rate of 50% in a U.S. population

(ranitidine trial), one may question whether gefarnate might actually be inferior to placebo (gefarnate < placebo). That is, does gefarnate actually hinder ulcer healing? If this were to be the case, then one cannot conclude from the relation, gefarnate < famotidine, that famotidine is necessarily superior to placebo; and the result of this study would not be able to provide the necessary supportive evidence for the efficacy claim.

Overall Conclusion

1. The acute phase of the domestic duodenal studies demonstrated that famotidine at the doses of 40 mg/hs, 20 mg/bid and 40 mg/bid were significantly more effective than placebo in the treatment of acute duodenal ulcers. The results of the acute phase of the ranitidine-controlled international study together with the arguments advanced by the sponsor provided supportive evidence to the claim that famotidine at these doses were superior to placebo.

2. Because essentially the same design (except endoscopies were scheduled at 3 and 6 months) as used by Glaxo in their ranitidine maintenance trial was employed in the two maintenance studies here, the same design issues may be raised here (See transcript of March 1985, G.I. Advisory Committee Meeting). That is, if famotidine merely relieves symptoms and accelerates healing without actually preventing recurrences, then under the present design with scheduled endoscopies relatively infrequent and far apart and with allowance for unscheduled endoscopy for cause, one would expect to observe fewer ulcers in the famotidine treated group. Therefore, it seems one still needs to know how much of the observed difference in recurrence rates may be attributed to differences between treatments in symptom relief and in healing rates and how much may actually be attributed to differences in relapse rates?

   Without being able to obtain such estimates, one cannot draw an unambiguous inference with respect to the prevention claim based on the results of these maintenance studies. Nevertheless, Dr. Lipicky has indicated that a maintenance claim could still be made if these studies can successfully demonstrate a significant treatment difference in both the observed proportions of unscheduled and scheduled ulcer relapses during the first period (0-3 months). This is based on the reasoning that if these conditions were met, then a patient certainly would benefit from a maintenance treatment because he would experience a relief of symptoms and his ulcers would heal faster, taking into consideration the relatively low safety risk associated with famotidine treatment.

3. Because of the early cutoff date for both the domestic and the international maintenance study, a bias might have been introduced into the observed recurrence rates on account of the fact that more placebo patients with symptomatic relapses would have data available by the cutoff date than famotidine patients. For domestic study, this bias may affect the observed recurrence rates for all three periods because about 25% of the patients had enrolled for less than 6 months and only about 22% had either completed or had the opportunity to complete the 12-month study. For the international study, this bias mainly affects the observed third

period (> 6 months) recurrence rates, because only about 5% of the patients at the time of this NDA submission had enrolled for less than 6 months, while close to 70% of the patients had either completed or had the opportunity to complete the 12-month study.

An accurate assessment of this bias would require more detailed information on symptom data which was not present in the domestic study and was not readily available in the submission for the international study.

In view of the above comments, the sponsor has been requested by this reviewer to provide tables of relapse rates at 3 and 6 months broken down by scheduled vs. unscheduled endoscopy. The sponsor has also been asked to make an assessment of the effect of the bias introduced by the early cutoff date on the recurrence rates in the first (3 months) and second (3-6 months) periods for the domestic study. Of course such assessment would not have become necessary, if the sponsor had submitted their analyses based on the completed studies.

Consequently, based on the available data at hand, one cannot recommend a 6-month maintenance claim for famotidine at the present time. A more definitive statement may be made after the sponsor has provided the above requested information. This will be discussed in a subsequent addendum.

4. The international gastric ulcer study showed that famotidine at 20 mg/bid was significantly superior to placebo at 4, 6 and 8 weeks in healing rates.

The Japanese gastric ulcer trial demonstrated that famotidine was significantly superior to gefarnate. Even though the sponsor considered gefarnate to be equivalent to placebo, this was not sufficient especially in view of the relatively low healing rates associated with gefarnate treatment. One needs to have well conducted trial(s) that demonstrate the equivalence of gefarnate and placebo (in a Japanese population?) and show that gefarnate is really no worse than placebo.

Comments Which May Be Conveyed to the Sponsor

Because of the flaw in the maintenance study design, one cannot draw an unambiguous inference with respect to the prevention claim based on the data collected from these studies. However, a maintenance claim may be made if these studies can successfully demonstrate a significant treatment difference in the observed proportion of unscheduled and scheduled ulcer relapses based on patient population at risk.

Therefore, in order to be able to make the maintenance claim for 6 months, the sponsor needs to provide tables and accompanying analyses of relapse rates at 3 and 6 months, broken down by scheduled vs. unscheduled endoscopy.

Furthermore, because of the bias introduced into the observed recurrence rates at 3 and 6 months in the domestic study due to the early cutoff date, an assessment of this bias would be necessary.

George Y.H. Chi, Ph.D.
Mathematical Statistician

cc:
Orig. 19-462 NDA
HFN-110
HFN-110/Dr. Bachrach
HFN-110/Dr. Lipicky
HFN-344/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Chi
Chron.
File: DRU 1.3.2 NDA
Dr. Chi/x34594/njs/sn/04/01/86/#0442n

Concur: Dr. Dubey

TABLE 1
Selected Characteristics of Treatment Groups at Baseline
(Domestic Duodenal Ulcer Study - Acute Phase)

Characteristic		Famotidine 40 mg/hs		Famotidine 20 mg/bid		Famotidine 40 mg/bid		Placebo	
Sex	Male	75	(78%)	69	(78%)	81	(82%)	76	(76%)
	Female	12	(22%)	20	(22%)	18	(18%)	24	(24%)
Smoking	Yes	58	(60%)	52	(58%)	59	(60%)	61	(61%)
	No	38	(40%)	37	(42%)	40	(40%)	39	(39%)
Drinking	Yes	18	(19%)	12	(13%)	14	(14%)	13	(13%)
	No	78	(81%)	77	(87%)	85	(86%)	87	(87%)
Initial Ulcer Size (cm)		0.86		0.91		0.88		0.86	
Number of Ulcers	1	79	(82%)	73	(82%)	88	(89%)	82	(87%)
	2+	17	(18%)	16	(18%)	11	(11%)	13	(13%)
Age at 1st Ulcer	Mean	37.9		40.6		35.8		39.7	
Duration of Ulcer (Years)		7.7		6.7		7.8		6.7	
Ulcer History	0	30	(31%)	42	(47%)	34	(34%)	26	(26%)
	1	22	(23%)	19	(21%)	24	(24%)	30	(30%)
	2+	44	(46%)	28	(31%)	41	(42%)	44	(44%)
Esophagus Condition	Yes	24	(25%)	27	(30%)	20	(20%)	33	(33%)
	No	72	(75%)	62	(70%)	79	(80%)	67	(67%)

TABLE 2
Crude and Kaplan-Meier Estimated Cumulative Healing Rates
(Domestic Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Treatment	Type of Estimate	N	Time of Endoscopy Week 2	Week 4	Week 8	End of Study
40 mg/hs	Crude	89	28 (32%)*	62 (70%)*	74 (83%)*	75 (84%)*
	Kaplan-Meier		32%*	72%*	88%*	90%*
	Dropouts		5	3	1	0
20 mg/bid	Crude	84	32 (38%)*	56 (67%)*	69 (82%)*	69 (82%)*
	Kaplain-Meier		38%*	70%*	89%*	89%*
	Dropouts		6	2	1	0
40 mg/bid	Crude	93	32 (34%)*	70 (75%)*	76 (82%)*	77 (83%)*
	Kaplan-Meier		34%*	79%*	89%*	90%*
	Dropouts		5	5	0	0
Placebo	Crude	97	16 (17%)	30 (31%)	44 (45%)	44 (45%)
	Kaplan-Meier		17%	33%	55%	55%
	Dropouts		11	15	4	0

* All rates were significantly higher than the coresponding placeo healing rates ($p < 0.05$)

TABLE 3
Frequency and Percent of Patients with Ulcer Healed
Stratified by Selected Factors
(Domestic Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Factor	Level	Treatment			
		40 mg/hs	20 mg/bid	40 mg/bid	Placebo
Ulcer size (cm)	0.5-0.9	45/50 (90%)	37/43 (86%)	37/48 (77%)	29/54 (54%)
	1.0-1.4	22/28 (79%)	18/26 (69%)	25/30 (87%)	13/31 (42%)
	1.5-2.5	8/11 (73%)	14/15 (93%)	14/15 (93%)	2/12 (17%)
Ulcer History	None	26/29 (90%)	34/40 (85%)	27/31 (87%)	14/25 ([illegible])
	Single	18/22 (82%)	16/19 (84%)	19/23 (83%)	15/29 ([illegible])
	Multiple	31/38 (82%)	19/25 (76%)	31/39 (80%)	15/43 (35%)
Esophagus Condition	Normal	56/67 (84%)	47/57 (83%)	62/76 (82%)	25/66 (38%)
	Abnormal	19/22 (86%)	22/27 (82%)	15/17 (88%)	19/31 (61%)
Drinking	No	59/71 (83%)	58/72 (81%)	66/79 (84%)	34/84 (41%)
	Yes	16/18 (89%)	11/12 (92%)	11/14 (79%)	10/13 (77%)
Smoking	No	30/34 (88%)	29/33 (88%)	31/37 (84%)	19/38 (50%)
	Yes	45/55 (82%)	40/51 (78%)	46/56 (82%)	25/59 (42%)
No. of Ulcers	1	64/74 (87%)	56/69 (81%)	67/82 (82%)	40/84 (48%)
	24	11/15 (73%)	13/15 (87%)	10/11 (91%)	4/13 (31%)

TABLE 4
Day and Night Pain Relief for the Treatment Groups at the End of Acute Phase
(Domestic Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

	Famotidine			
	40 mg/hs (39)	20 mg/bid (84)	40 mg/bid (93)	Placebo (97)
Day Pain				
No. of Patients with Pain Relief	86%*	78%*	80%*	53%
Median Time (days) to Pain Relief	11*	15*	9*	54
Night Pain				
No. of Patients with Pain Relief	87%*	77%*	91%*	56%
Median Time (days) to Pain Relief	10*	15*	6*	52

* Significantly different from placebo ($p < 0.001$)

TABLE 5
Antacid Consumption by Treatment Groups
(Domestic Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Treatment	(N)	Week 1	(N)	Week 2	(N)	Week 4	(N)	Week 8
Mean No. of Antacid Tablets								
40 mg/hs	(92)	1.7**	(87)	1.4**	(56)	1.0**	(21)	1.2
20 mg/bid	(84)	1.9	(80)	1.2**	(45)	1.0**	(18)	0.7**
40 mg/bid	(93)	1.5**	(84)	0.9**	(51)	0.6**	(12)	0.3*
Placebo	(98)	2.2	(95)	2.1	(70)	1.7	(37)	1.4
Mean Days of Antacid Therapy								
40 mg/hs	(92)	3.3	(87)	2.7**	(56)	2.2**	(21)	2.9
20 mg/bid	(84)	3.5	(80)	2.5**	(45)	1.9**	(18)	1.0**
40 mg/bid	(93)	2.9**	(84)	2.0**	(51)	1.3**	(12)	0.8**
Placebo	(98)	4.1	(95)	3.6	(70)	3.3	(37)	2.8

*,** Significantly different from placebo $p < 0.05$, $p < 0.01$

TABLE 6
Selected Characteristics of Treatment Groups at Baseline
(Domestic Duodenal Ulcer Study - Maintenance Phase)

Characteristic	Famotidine 40 mg/hs (54)	Famotidine 20 mg/hs (57)	Placebo (66)
Age (Years)			
Mean	51**	47	43
Sex			
Males	14 (26%)	15 (26%)	17 (26%)
Females	40 (74%)	42 (74%)	49 (74%)
Treatment During Acute Phase			
40 mg/hs	14 (26%)	18 (32%)	17 (26%)
20 mg/bid	16 (30%)	15 (26%)	12 (18%)
40 mg/bid	15 (28%)	16 (28%)	22 (33%)
Placebo	8 (17%)	7 (12%)	15 (23%)
Week During Which Ulcer Healed in Acute Study			
Week 2	29 (54%)[a]	26 (46%)	25 (38%)
Week 4	20 (37%)	20 (35%)	31 (47%)
Week 8	5 (9%)	11 (19%)	10 (15%)
Smoking			
Yes	31 (57%)[b]	40 (70%)	42 (64%)
No	23 (43%)	17 (30%)	24 (36%)
Drinking			
Yes	12 (22%)	8 (14%)	14 (21%)
No	42 (79%)	49 (86%)	52 (79%)
Initial Ulcer Size			
Mean (cm)	0.82	0.89	0.92

** Significantly different from placebo, $p < 0.01$
a,b different from placebo, $p=0.08$, $p=0.10$ respectively

TABLE 7
Duodenal Ulcer Relapse Rates by Treatment Groups
(Domestic Duodenal Ulcer Study - Maintenance Phase)
"Per Protocol"

Time		Famotidine 40 mg/hs	Famotidine 20 mg/hs	Placebo
Period 1 (Days 1-42)	No. Relapsed	0 (0%)	1 (2%)	8 (13%)
	No. Dropped out	8+	5+	11+
	Total number	49	49	62
	Cumulative Relapse Rate	0%**	2%*	13%
Period 2 (Days 43-105)	No. Relapsed	7 (17%)**	8 (19%)*	20 (47%)
	No. Dropped out	15+	8+	6+
	Total Number	41	43	43
	Cumulative Relapse Rate	17%**	20%**	53%
Period 3 (Days 106+)	No. Relapsed	3 (16%)[a]	2 (7%)**	6 (35%)
	No. Dropped out	16+	25+	11+
	Total Number	19	27	17
	Cumulative Relapse Rate	30%**	26%**	70%

*,** significantly different from placebo, $p < 0.05$, $p < 0.01$ respectively
a different from placebo, $p=0.09$
+ a large number of these patients had been in the maintenance phase for less than the required length of time and are still continuing in the study.

TABLE 8
Crude and Kaplan-Meier Estimated Cumulative Healing Rates
(International Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Treatment	Type of Estimate	N	Time of Endoscopy Week 4	Week 6	Week 8	End of Study
40 mg/hs	Crude	240	82 (34%)	164 (68%)	210 (87%)	211 (88%)
	Kaplan-Meier		34%	71%	92%	93%
	Dropouts		12	3	1	0
20 mg/bid	Crude	247	94 (38%)	191 (77%)*	228 (92%)	231 (93%)*
	Kaplan-Meier		38%	79%	95%	96%
	Dropouts		6	2	0	0
40 mg/bid	Crude	247	109 (44%)*	201(81%)*	227 (92%)	231 (93%)*
	Kaplan-Meier		44%	85%	97%	98%+
	Dropouts		12	1	0	0
150 mg/bid	Crude	246	96 (39%)	186 (76%)	222 (90%)	223 (91%)
	Kaplan-Meier		39%	77%	94%	94%
	Dropouts		7	3	2	0

* significantly better than 40 mg/hs, $p < 0.05$
+ significantly better than all other treatment groups, $p < 0.05$

TABLE 9

Day and Night Pain Relief for the Treatment Groups at the End of Acute Phase
(International Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

	Famotidine 40 mg/hs	Famotidine 20 mg/bid	Ranitidine 40 mg/bid	Ranitidine 150 mg/bid
Day Pain				
No. of Patients with Pain Relief	81%	85%	81%	81%
Median Time (days) to Pain Relief	7.0	6.0	6.0	7.0
Night Pain				
No. of Patients with Pain Relief	85%	90%	88%	82%
Median Time (days) to Pain Relief	3.5	3.0**	3.0**	5.0

** significantly shorter than the ranitidine group, $p < 0.01$

TABLE 10
Antacid Therapy by Treatment Group
(International Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Mean Day of Antacid Therapy No. of Patients (%)	Week 1	Week 2	Week 4	Week 8
Famotidine				
40 mg/hs	2.0 100/241 (41%)	1.3 62/227 (28%)	0.8 22/132 (17%)	0.7 8/53 (15%)
20 mg/bid	1.6** 92/250 (37%)	0.9** 58/239 (24%)	1.0 24/140 (17%)	0.2 1/41 (2%)
40 mg/bid	1.7* 99/249 (40%)	1.1* 58/237 (24%)*	0.7 19/113 (17%)	0.5 2/28 (7%)
Ranitidine				
150 mg/bid	2.3 116/247 (47%)	1.6 81/237 (34%)	1.2 31/129 (22%)	0.7 5/40 (13%)

*,** significantly different from ranitidine group, $p < 0.05$, $p < 0.01$

TABLE 11
Cumulative Duodenal Ulcer Relapse Rates by Treatment Groups
(International Duodenal Ulcer Study - Maintenance Phase)
"Per Protocol"

Time		Famotidine 20 mg/hs	Placebo
Period 1 (Days 1-42)	No. Relapsed	5 (1.9%)**	39 (12.7%)
	No. Dropped out	26 (10.0%)+	33 (10.8%)++
	Total Number	268	306
	Cumulative Relapse Rate	1.9%**	12.7%
Period 2 (Days 43-105)	No. Relapsed	38 (16.0%)**	127 (54.3%)
	No. Dropped out	17 (7.2%)	12 (5.1%)
	Total Number	237	234
	Cumulative Relapse Rate	17.6%**	60.1%
Period 3 (Days 106 +)	No. Relapsed	27 (14.8%)**	31 (32.6%)
	No. Dropped out	2 (0.6%)	4 (4.3%)
	Total Number	182	95
	Cumulative Relapse Rate	29.8%**	73.1%

** significantly different from placebo, $p < 0.01$

TABLE 12
Distribution of Day and Night Pain
(International Duodenal Ulcer Study - Maintnance Phase)
"Per Protocol"

Score	Day Pain		Night Pain	
	Famotidine (N=259)	Placebo (N=301)	Famotidine (N=259)	Placebo (N=301)
Baseline				
None	211 (81%)	265 (88%)	228 (87%)	280 (93%)
Mild	45 (17%)	34 (11%)	27 (10%)	18 (6%)
Moderate	3 (2%)	2 (1%)	3 (2%)	3 (1%)
Severe	0	0	0	0
End of Study				
None	189 (73%)	109 (36%)	217 (84%)	154 (51%)
Mild	39 (15%)	64 (21%)	26 (10%)	49 (16%)
Moderate	27 (10%)	85 (28%)	12 (5%)	59 (20%)
Severe	4 (2%)	43 (15%)	4 (2%)	39 (13%)

TABLE 13
Cumulative Gastric Ulcer Healing Rates
(International Gastric Ulcer Study)
"Per Protocol"

Treatment		Week 4	Week 6	Week 8	End of Study
Famotidine 40 mg/hs (N=149)	No. Healed	70 (47%)**	97 (65%)**	120 (80%)**	120 (80%)**
	No. Dropped out	11	2	0	
	Kaplan-Meier L.T. Estimate	47%	68%	87%**	87%
Placebo (N=145)	No. Healed	45 (31%)	67 (46%)	78 (54%)	80 (55%)
	No. Dropped out	16	10	1	
	Kaplan-Meier L.T. Estimate	31%	49%	60%	62%

** Significantly greater than placebo, $p < 0.01$

TABLE 14
Saicita and Miwa's Six-Stage Classification
of Ulcer Healing

A_1 - Acute gastric ulcer with depth, exudate and edematous margins. No evidence of epithelial regeneration at the ulcer margin.

A_2 - Same as A_1 but with less edema. Evidence of epithelial regeneration can be seen at the ulcer margin.

H_1 - An ulcer remains but is 50 to 65% smaller than A_1 with regenerating epithelium extending into the ulcer base.

H_2 - Futher evidence of regeneration with an exudate 25 to 33% the diameter of A_1.

S_1 - Complete epithelialization with reddened background.

S_2 - Color of scar now indistinguishable from that of surrounding mucosa.

An ulcer was considered as healed if it was in either stage S_1 or S_2, and unhealed otherwise

TABLE 15
Cumulative Gastric Ulcer Healing Rates at Weeks 4 and 8
(Japanese Gastric Ulcer Study)
"Per Protocol"

Treatment		Week 4	Week 8	End of Study
Famotidine 20 mg/bid (N=96)	No. Healed	19 (26.4%)**	46 (63.9%)**	54 (75.0%)**
	No. Dropped out	5	1	1
	Kaplan-Meier LT Estimate	28.1%**	68.6%**	80.1%**
Gefernate 100 mg/tid (N=96)	No. Healed	3 (4.0%)	18 (24.0%)	23 (30.7%)
	No. Dropped out	19	2	0
	Kaplan-Meier LT Estimate	4.8%	32.5%	40.4%

** significantly greater than gefarnate, $p < 0.01$

Statistical Review and Evaluation
(Addendum)

NDA #: 19-467/Drug Class: 1C

Applicant: Merck, Sharp & Dohme Research Laboratories

Name of Drug: PEPCID (Famotidine) 40 mg/hs

Indication:

For treatment of active duodenal ulcers, gastric ulcers, the prophylactic use in duodenal ulcer disease, and the treatment of pathological hypersecretory conditions such as Zollinger-Ellison Syndrome.

Documents received:

Documents dated February 14, 1986, providing a breakdown of the ulcer relapse data in the U.S. and international duodenal ulcer maintenance studies by scheduled vs. unscheduled endoscopies based on the completed 12 month data, and one of two volumes dated March 4, 1986, providing arguments showing that gefarnate is superior to placebo.

A. On the Duodenal Ulcer Maintenance Studies

1. A Design Issue with Respect to the Prevention Claim

The principal hypothesis that was being tested in the duodenal prevention trials is that excessive nocturnal gastric acid secretion is the primary factor in the patnogenesis of duodenal ulcer. It was theorized that by inhibiting or controlling the amount of nocturnal gastric acid secretion with famotidine, one would induce an unfavorable condition for the normal development of duodenal ulcers. In the sponsor's trials, patients whose ulcers had just healed in an acute trial were randomized to either a famotidine or a placebo arm. They were endoscoped at 3, 6, or 12 months or at unscheduled times at the discretion of the investigator if they reported symptoms suggestive of the presence of ulcers or for administrative reasons. Patients found to have an ulcer at any of these endoscopies were discontinued from the trial. The sponsor hoped to demonstrate ulcer prevention by showing that the cumulative proportion of patients with relapses at these prescheduled time points was significantly lower among the famotidine treated patients than among the placebo treated patients.

Under the sponsor's design, because scheduled endoscopies were relatively infrequent and far apart, an asymptomatic or mildly symptomatic ulcer may have recurred and rehealed before the next scheduled endoscopy and hence escaped detection. If an ulcer did recur, then it would be less likely to be observed under the famotidine treatment than under the placebo treatment because it has been demonstrated in the acute trials that famotidine relieved symptoms and healed ulcers faster than placebo (assuming, not unreasonably, that the maintenance dose of 20 mg/hs of famotidine is also a therapeutic dose). Therefore, in order to be able to make the prevention claim, one needs to be

able to estimate the amount of the observed treatment difference in the cumulative proportions of patients with relapses at the prescheduled times can actually be attributed to prevention. Since these trials did not provide the information needed for such estimates, one cannot draw at the present time an unambiguous inference with respect to ulcer prevention.

2. The Requirements for a Maintenance Claim

The content of this section reflects the conclusion reached in a recent discussion with Dr. Lipicky. Without sufficient information to be able to definitively conclude that famotidine prevented duodenal ulcer recurrence, a maintenance claim can still be made only if it can be demonstrated that maintenance therapy was beneficial to the patients with relatively low safety risk.

Within the context of the current design, a maintenance claim can be made for famotidine if these studies can successfully demonstrate a significant treatment difference in the observed proportions of both the unscheduled (mainly symptomatic) and the scheduled ulcer relapses in the first period. The rationale for these requirements is as follows:

Merely observing a significant treatment difference in the proportion of unscheduled (mainly symptomatic) relapses, but not in the scheduled relapses is not sufficient to establish a maintenance claim, because such result may be observed from a drug that simply relieves symptoms but does not accelerate healing and prevent recurrence. Thus, putting a patient on a maintenance therapy with such drug would be unwise because of the attendant risks involved in not treating an asymptomatic ulcer. On the other hand, merely observing a significant treatment difference in the proportion of scheduled relapses but not in the unscheduled relapses is not sufficient either, because such result may be anticipated of a drug that accelerates healing but does not relieve symptoms and prevent recurrence. For such drug, one should just treat the patient when an ulcer is detected and maintenance therapy should not be recommended. Whereas if both conditions were met, then a patient certainly would benefit from a maintenance treatment because he would experience a relief of symptoms and his ulcers would heal faster. It is sufficient to satisfy these requirements for the first period (0-3 months) because available evidence suggests that a preponderance of the observed relapses occurred early during the trial (51% of famotidine relapses and 71% of placebo relapses from U.S. Study and 45% of famotidine relapses and 78% of placebo relapses from the International Study occurred in the first period) and because dropping out these relapsers during the first period would make the treatment groups not quite comparable in the later periods (unless the first period was relatively short and not too many patients were dropped out, then the requirements may have to be satisfied for at least the first two periods. In any event, the results of the later periods can always be used as supportive evidence).

3. Study Results in Support of a Maintenance Claim

For the purpose of establishing the maintenance claim, only the two placebo-controlled maintenance studies 301 and 301C will be discussed here. The safety profile of famotidine has been discussed in the medical review by Dr. Bachrach.

The U.S. Study (see Table 1) demonstrated that famotidine patients had significantly lower proportion of unscheduled relapses (2.1% for famotidine 40 mg/hs and 1.1% for famotidine 20 mg/bid during the first 3 months than the placebo patients (20.5%, $p < 0.001$). Similarly, the famotidine patients also had a significantly lower proportion of scheduled relapses (9.4% for famotidine 40 mg/hs and 14.1% for famotidine 20 mg/bid) at 3 months than the placebo patients (28.6%, $p < 0.005$, $p < 0.05$). The same trend was observed for both the unscheduled and the scheduled relapses during the second period (4 - 6 months) with statistical significance achieved ($p < 0.05$) for the unscheduled relapses. The trend was evident in the third period but failed to reach statistical significance.

The International Study (see Table 2) demonstrated that during the first 3 months, famotidine patients had significantly fewer unscheduled relapses (4.4%) than placebo patients (21.8%, $p < 0.001$) and also significantly fewer scheduled relapses (13.0%) than placebo patients (51.3%, $p < 0.001$). The same trend was observed for the second period with statistical significance achieved at $p < 0.01$ and 0.03 for the unscheduled and scheduled, respectively. The same trend was also evident in the third period but failed to achieve significance at the 0.05 level.

Therefore, based on the results of these two placebo-controlled studies and the safety profile for famotidine, a maintenance claim can be recommended for famotidine 40 mg/hs in the long term treatment of duodenal ulcer disease.

B. On the Gastric Ulcers

1. Gefarnate is a marketed drug in Japan. Yet there is only one (presumably Japanese) trial comparing gefarnate to placebo. As shown in Table 3 provided by the sponsor, this trial failed to differentiate between gefarnate and placebo.

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George Y.H. Chi, Ph.D.
Group I Leader (Acting)

cc:
Orig.
HFN-110
HFN-110/Dr. Lipicky
HFN-110/Dr. Bachrach
HFN-344/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Chi ✓
Chron.
File: DRU 1.3.2 NDA
Dr. Chi/x34594/pcf/njs/04/11/86/#0658n

Concur: Dr. Dubey 4/15/86

Table 1
U.S. Duodenal Ulcer Maintenance Study

Treatment	Ulcer Relapse	0-3 Months (0.3)	0-3 Months 3	3-6 Months (3, 6)	3-6 Months 6	6-12 Months (6, 12)	6-12 Months 12
Famotidine 40 mg/hs	Observed	2 (2.1%)	8 (9.4%)	2 (2.8%)	8 (11.8%)	1 (2.6%)	2 (6.3%)
	Not observed	95	77	70	60	38	30
	Not Evaluable	9	10*	4	2*	5	2*
	Total	106	95	76	70	44	34
Famotidine 20 mg/bid	Observed	1 (1.1%)	11 (14.1%)	1 (1.4%)	3 (4.5%)	1 (2.3%)	3 (7.0%)
	Not observed	89	67	70	64	44	40
	Not Evaluable	7	11*	1	3*	6	0*
	Total	97	89	72	70	51	43
Placebo	Observed	18 (20.5%)	18 (28.6%)	6 (13.6%)	4 (11.7%)	3 (13.6%)	2 (10.5%)
	Not observed	70	45	38	30	19	17
	Not Evaluable	11	7*	1	3*	1	0*
	Total	99	70	45	37	23	19
Two-sided p-value Chi-square test	40 mg/hs vs. Placebo	p<0.001	p<0.005	p<0.05	p<0.10	p<0.10	[illegible]
	20 mg/bid vs. Placebo	p<0.001	p<0.05	p<0.01	p<0.10	p<0.10	p<0.10

*Including patients who did not have scheduled endoscopies

Table 2
International Duodenal Ulcer Maintenance Study

Treatment	Ulcer Relapse	0-3 Months (0.3)	0-3 Months 3	3-6 Months (3, 6)	3-6 Months 6	6-12 Months (6, 12)	6-12 Months 12
Famotidine 20 mg/bid	Observed	14 (4.4%)	35 (13.0%)	9 (3.7%)	31 (13.5%)	9 (6.0%)	11 (8.3%)
	Not observed	301	234	236	198	141	122
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	Total	352	301	250	236	158	140
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	Not observed	251	109	107	77	38	30
	Not Evaluable	42	27*	3	4*	4	1*
	Total	363	251	124	106	47	38
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Comparison of Gefarnate to Placebo in a Gastric Ulcer Trial
(Japan?)

	Healed	Not Healed	Total
Gefarnate	9 (39%)	14	23
Placebo	5 (21%)	19	24

$\chi^2 = 1.84$
$p > 0.15$

Statistical Review and Evaluation
(Addendum)

NDA #: 19-467/Drug Class: 1C

Applicant: Merck, Sharp & Dohme Research Laboratories

Name of Drug: PEPCID (Famotidine) 40 mg/hs

Indication:

For treatment of active duodenal ulcers, gastric ulcers, the prophylactic use in duodenal ulcer disease, and the treatment of pathological hypersecretory conditions such as Zollinger-Ellison Syndrome.

Documents received:

Documents dated February 14, 1986, providing a breakdown of the ulcer relapse data in the U.S. and international duodenal ulcer maintenance studies by scheduled vs. unscheduled endoscopies based on the completed 12 month data, and one of two volumes dated March 4, 1986, providing arguments showing that getarnate is superior to placebo.

A. On the Duodenal Ulcer Maintenance Studies

1. A Design Issue with Respect to the Prevention Claim

The principal hypothesis that was being tested in the duodenal prevention trials is that excessive nocturnal gastric acid secretion is the primary factor in the patnogenesis of duodenal ulcer. It was theorized that by inhibiting or controlling the amount of nocturnal gastric acid secretion with famotidine, one would induce an unfavorable condition for the normal development of duodenal ulcers. In the sponsor's trials, patients whose ulcers had just healed in an acute trial were randomized to either a famotidine or a placebo arm. They were endoscoped at 3, 6, or 12 months or at unscheduled times at the discretion of the investigator if they reported symptoms suggestive of the presence of ulcers or for administrative reasons. Patients found to have an ulcer at any of these endoscopies were discontinued from the trial. The sponsor hoped to demonstrate ulcer prevention by showing that the cumulative proportion of patients with relapses at these prescheduled time points was significantly lower among the famotidine treated patients than among the placebo treated patients.

Under the sponsor's design, because scheduled endoscopies were relatively infrequent and far apart, an asymptomatic or mildly symptomatic ulcer may have recurred and rehealed before the next scheduled endoscopy and hence escaped detection. If an ulcer did recur, then it would be less likely to be observed under the famotidine treatment than under the placebo treatment because it has been demonstrated in the acute trials that famotidine relieved symptoms and healed ulcers faster than placebo (assuming, not unreasonably, that the maintenance dose of 20 mg/hs of famotidine is also a therapeutic dose). Therefore, in order to be able to make the prevention claim, one needs to be

able to estimate the amount of the observed treatment difference in the cumulative proportions of patients with relapses at the prescheduled times can actually be attributed to prevention. Since these trials did not provide the information needed for such estimates, one cannot draw at the present time an unambiguous inference with respect to ulcer prevention.

2. The Requirements for a Maintenance Claim

The content of this section reflects the conclusion reached in a recent discussion with Dr. Lipicky. Without sufficient information to be able to definitively conclude that famotidine prevented duodenal ulcer recurrence, a maintenance claim can still be made only if it can be demonstrated that maintenance therapy was beneficial to the patients with relatively low safety risk.

Within the context of the current design, a maintenance claim can be made for famotidine if these studies can successfully demonstrate a significant treatment difference in the observed proportions of both the unscheduled (mainly symptomatic) and the scheduled ulcer relapses in the first period. The rationale for these requirements is as follows:

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Concur: Dr. Dubey

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IMAGE EVALUATION
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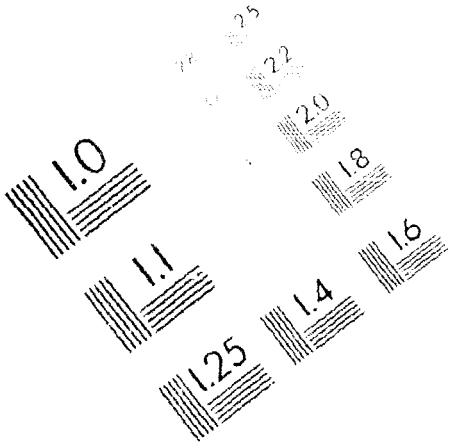

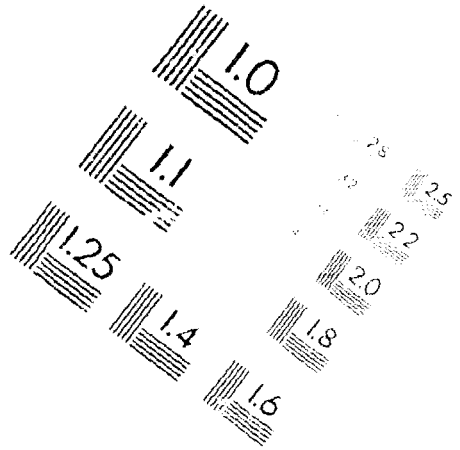

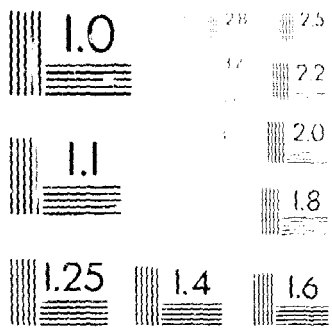

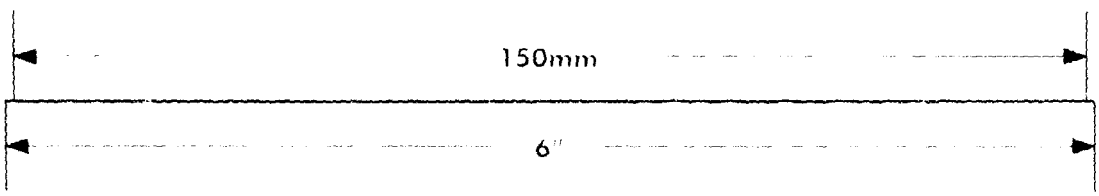

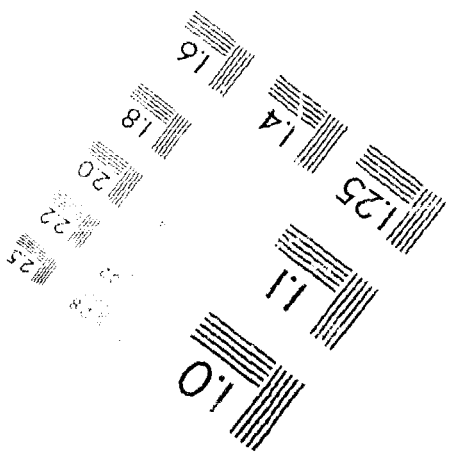

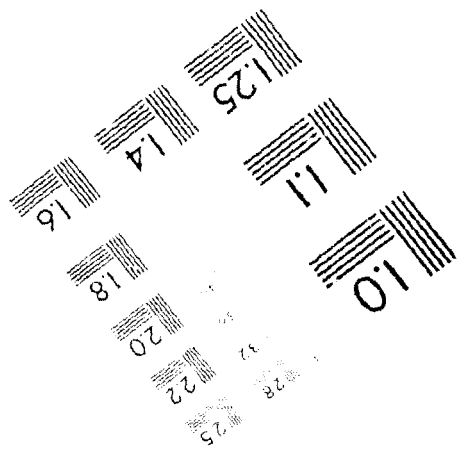

APPLIED IMAGE
1653 E. MAIN STREET
ROCHESTER, NY 14609
TEL (716) 482-0300
FAX (716) 288-5989

NDA
19462

UDA

1962

AP LTR

OCT 15 1986

NDA 19-462

Merck Sharp & Dohme Research Laboratories
Division of Merck & Co.
Attention: Gerard D. Picot, Ph.D.
West Point, PA 19486

Dear Dr. Picot:

Please refer to your June 24, 1985 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pepcid (famotidine) Tablets.

We also acknowledge receipt of your amendments dated October 3 and 7, 1986.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on October 7, 1986. Accordingly, the application is approved.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Constance Burner Henry
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-100/Dr. Temple
HFN-232 (with labeling)
HFN-110/CHenry/10/9/86;10/10/86;10/10/86
sb/10/10/86;10/10/86;10/14/86;10/14/86/ssss
R/D: NMorgenstern/10/10/86
RLipicky/10/10/86;10/14/86
PDeslauriers/10/10/86
WBachrach/10/10/86
RWolters/10/10/86;10/14/86

APPROVAL

NDA

19462

AE LTR

SEP 30 1986

NDA 19-466

Merck Sharp and Dohme Research Laboratories
Attention: Girard Picot, Ph.D.
Division of Merck and Co., Inc.
West Point, PA 19486

Dear Dr. Picot:

Please refer to your June 24, 1985 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pepcid (famotidine) Tablets.

We also acknowledge receipt of your amendments dated August 9, September 30 (two), October 15 and 24, November 7, 13, 18 and 22; December 13, 18 and 20, 1985; January 9, 10, 14 and 16; February 14 and 24; March 4, 18 (two) and 27; April 3, 8 and 21; May 7 and 22; August 7; and September 26, 1986.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit final printed labeling for the drug. The labeling should be consistent with the content of the enclosed marked up draft and should address the following issue: The decrease in drug clearance and increased half-life with decreased renal function is well-documented. Your dosage recommendation is to adjust for this by increasing the dosing interval to 36-48 hours. It is not obvious that this is the best possible response, i.e., the one that would best match the effect of a 40 mg HS dose in normals, i.e., a dose reduction to 20 mg would also be possible. Please examine these alternatives, simulating them as necessary, and reconsider the dosing recommendation. If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Division of Drug Advertising and Labeling, HFN-240
Room 10B-04
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit twelve copies of the printed labels and other labeling seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Constance Burner Henry
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Enclosure

cc:
Original NDA
HFN-110
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HFN-83
HFN-100/Dr. Temple
HFN-110/THassall/5/20/86;5/28/86;5/29/86;7/28/86
sb/5/27/86;5/28/86;7/28/86;9/25/86/3639s
R/D: RLipicky/5/30/86;7/28/86
CResnick/5/29/86
RWolters/6/9/86;7/29/86
WBachrach/6/9/86;7/30/86
NMorgenstern/6/9/86;7/30/86
GJohnson for CAR/7/29/86
VGlocklin/8/1/86
CKumkumian/8/5/86

APPROVABLE

FOR FOI PURPOSES - DELETE PARAGRAPHS 4, 5 AND 6.

NDA
19462

Pharm
REV

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

NDA 19-462 Pepcid (famotidine)

August 26, 1985
Merck Sharpe & Dohme

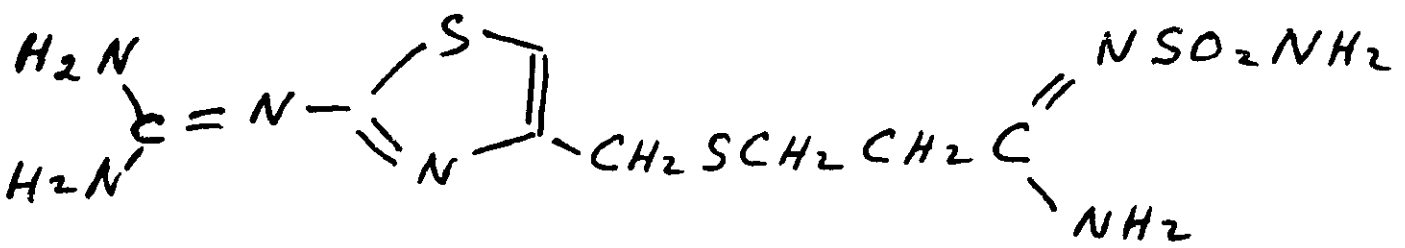
ORIGINAL SUBMISSION CD&B RECEIPT DATE: 6/24/85

Pharmacology Review
(Original Summary)

1. Name of Drug: Pepcid (famotidine) or MK-208

2. Category: Histamine H2 receptor antagonist

3. Chemical Structure:



Famotidine

4. Composition and Dosage Form:

	mg/per tablet
Famotidine.....	20 or 40
plus inactive ingredients	

5. Indications: Short-term treatment of active duodenal and gastric ulcers, long-term prevention of duodenal ulcer recurrence, and long-term management of pathological hypersecretory conditions such as Z-E Syndrome.

6. Dosage: Recommended adult dose is 40mg at bedtime for acute duodenal or gastric ulcer. The maintenance dose to prevent ulcer recurrence is 20mg at bedtime. For Z-E the dose is usually 20mg q.i.d. but could range up to 160mg q.i.d. In patients with renal insufficiency, dosing may be every other day for whatever indication.

7. IND UNDER WHICH CLINICAL STUDIES CONDUCTED: [redacted]

8. Submitted Preclinical Data: These studies were largely conducted either by Yamanouchi Pharm. of Japan (Y) or Merck Sharpe & Dohme (MSD). Many of these studies were reviewed in the past in conjunction with IND 18,888. The following summarizes preclinical data that have not been previously reviewed. For the sake of brevity, the letters F, C, and R are used for Famotidine, Cimetidine, and Ranitidine respectively.

A) Acute Toxicity:

Dogs:

Four dogs treated at separate times with single oral doses ranging from 10 to 2000mg/kg showed no adverse effects (clinical, ECG, serum biochem, body weight, hematology, urinalysis). When the same dogs were subsequently tested for 15 consecutive days with 1000mg/kg/day, they exhibited only slight weight loss and necropsy was normal.

Another set of dogs were tested acutely i.v. with a 2 or 3% formulation containing saline and L-Aspartic acid at doses ranging from 10 to 300 mg/kg injected at the rate of 10 ml/minute. No deaths occurred up to 200 mg/kg but one died at 300 mg/kg of unknown cause. The dose of 10 mg/kg i.v. caused no clinical reactions, but 30 & 100 mg/kg elicited emesis in 1/4 & 4/4 respectively. Clinical reactions at 200 mg/kg & higher were emesis, weakness, defecation, lacrimation, and sometimes conjunctival injection, inactivity, & prone posture at 300 mg/kg. Slight tachycardia occurred at 300 mg/kg, glucosuria & proteinuria at 100, 200, and 300 mg/kg, prominent GOT & GPT at 200 and 300 mg/kg, & hypokalemia at 300 mg/kg. Gross & microscopic exam were reportedly normal.

Rats: The injectable formulation of F when tested for acute i.v. toxicity in mice after exposure to conditions of degradation (2 months at 60°C) displayed an LD50 (410 mg/kg) which was comparable to undegraded material (306-438 mg/kg).

Six analogues of F which are either byproducts of synthesis or products of degradation were tested for acute toxicity. All showed either low toxicity or toxicity comparable to F except for one (A-4) It showed an LD50 of only 113 mg/kg and 225 mg/kg orally in mice and rats and an LD50 i.v. of 22 mg/kg and 18 mg/kg in same. However when a mixture of F and all of the 6 analogues, each analogue at a conc 5 times the expected, the oral LD50 of this mixture in mice was the same as normally manufactured material, i.e. 8000 mg/kg. A-4, which is a byproduct in the synthesis of MK-208, was nephrotoxic in rats treated acutely p.o.

B. Subacute Toxicity:

Rats In an i.v. study conducted by Huntingdon Research Groups of 15M and 15F rats were injected daily with 0, 4, 20, 100, or 200 mg/kg of F for 13 weeks.

Results

Clinical reactions following injection were observed in rats injected with 100 & 200 mg/kg. These included tremors, labored breathing, unsteady gait, pallor, and salivation. Survival was reduced at the top dose (4M & 5F deaths). Growth depression & increased water consumption was seen at the upper two levels, as well as anemia and slight increases in urea nitrogen and creatinine (the latter at 200). At necropsy, severe reactions were seen at the injection sites of 200 mg/kg treated animals and renal cortical scarring was seen in 5/15 and 10/11 male rats al 100 & 200 mg/kg. Stomach weights were increased at the upper two levels & adrenal weights in males treated with 200 mg/kg. Microscopic studies confirmed the gross finding in the injection sites at the top dose & the renal effects (foci of basophilic tubules or tubules with flattened epithelium in 3/15, 3/10, 3/10, 7/10, and 11/11 male rats of the C, L, M, + H levels). The concentration of drug used at the top dose was 3.3% (.07 to 1.7% at the lower levels which did not show undue irritation histologically). The stomachs were said to be normal histologically.

Dogs: In a range-finding study conducted by Y beagles were injected I.v. with 0, 100 and 200 mg/kg/day of F for 2 wks. The injection rate was 10 or 20 ml/minute and the conc. of the drug was 2%.

Results: No deaths occurred but distnict clinical reactions were elicited in a dose related way. The reactions were emesis, salivation, conjunctival injection (top dose), collapse (top dose after injection) & associated defecation. No other effect (including biochemical, gross & histological) were seen.

C. Chronic Studies:

Rats

1) In a study conducted by MSD to evaluate the reversibility of eosinophilic cytoplasmic granularity (ECG) of gastric chief cells, groups of 60 male S-D rats were gavaged with 0 or 2000 mg/kg/day of F for 182 days. Twenty rats per group were sacrificed at term (182 days) and the remainder after a 14 wk recovery period.

Results

After 182 days slight ECG of chief cells was seen in 5/24 (21%) controls and 14/20 (70%) treated. After the 14 wk recovery period the incidence was 11/36 (31%) controls and 11/40 (28%) treated, thus indicating reversibility of the effect.

2) A second reversibility study was conducted by Y in two groups of 60 M CRCD rats at oral doses of 0 and 200 mg/kg. Treatment lasted 24 wks & the post-treatment recovery period was 18 wks. Another reversibility study conducted by Y in SD rats entailed the oral administration by gavage of 0 or 2000 mg/kg of F to two groups of 70 to 107 rats for up to 43 wks. Interim autopsies were made at weeks 13, 26, 37 & 39 and at 5 & 13 wks post drug (recovery phase). Subgroups included controls and test animals receiving acid drinking water for 43 wks, at which time they were sacrificed. A fourth reversibility study was done (see below).

Results

In the first study gastric chief cell eosinophilic granularity (ECG) was observed in 10/16 and 11/17 animals treated with 200 mg/kg of F for 14 & 22 wks vs. 0/15 & 1/17 controls at corresponding times. Sixteen weeks after discontinuation of treatment in week 24, the incidence of ECG was 1/27 & 1/28 in the treated & controls respectively.

In the second study, the number of incidence ECG cells as cell as the intensity of ECG cell proliferation increased in the drug treated animals as early as 13 wks; these effects intensified over the course of treatment. HCl acid in the drinking water did not prevent or enhance the ECG cell proliferation in the drug treated. There was partial regression of the enhanced number of ECG cells in the test animals 13 wks after cessation of treatment.

In the third study, the ECG cell hyperplasia noted in rats tested for 43 wks was totally reversed 26 wks subsequently.

Dogs:

1) In a 26 week i.v. study conducted by Y groups of 4M & 4F beagles were injected daily with 0, 4, 25, or 100 mg/kg/day. The formulation used was a lyophilized preparation containing L-aspartic acid and dissolved in saline at a conc. of 2%.

Results

One dog at 100 mg/kg collapsed 2 minutes after the first injection & displayed reduced motor activity, decreased respiratory rate, pale mucus membranes & weak pulse. It recovered 3.5 hrs. after injection.

Dose related emesis occurred minutes after injection. Salivation occurred at the top dose as well as reddening of mouth and ears, possibly due to vasodilation , occasionally in 3/8 dogs.

The pulse rate of nearly all high dose dogs was prominently increased 1-3 minutes after injection during the entire study, but were unchanged at the lower doses (5 & 25mg/kg).

No adverse effects were seen in any of the other parameters (water intake, opthalmologic, serum biochem, hematology, myelographic, urinalysis). Injection sites were not unduly affected.

2) In a study identical to the previous one, groups of beagles were injected with 0, 5, 25, or 100 mg/kg for 26 wks; this study was conducted by Shin Nippon Labs.

Results

The results of this study were essentially identical to the previous one. The only notable differences was the presence of mucosal reddening (vasodilation) & slight tachycardia at the 25 mg/kg level as well as at the top dose and the absence of collapse of any treated dog.

D. Reproduction Studies:

1. Fertility & General Reproductive Performance: In a study (#81106) conducted by Y groups of 24M & 48F Sprague-Dawley rats were gavaged daily with 0,500, 1000, 12000 mg/kg for 12 weeks prior to mating & through mating in the case of the males & for 2 wks before mating, through mating & up to day 13 of gestation for 1/4 of the females, or up to day 20 for 1/2 of the females, or through natural delivery & up to weaning for 1/4 of the females. The development & reproductive capacity of the F1 generation was determined & the early growth of the F2 generation. Teratogenicity was determined by examination of the offspring delivered surgically at day 20 of gestation for gross, visceral, and skeletal defects.

Results

None of the test doses produced drastic impairment. Treated responded essentially like controls with respect to mating performance, fertility, fecundity, growth, development & fertility of the F1 generation, and status of the F2 generation. Nor was there any indication of teratogenicity, although the drug appeared to cause minor skeletal variations (increased ribs, sternebrae, and caudal vertebrae). The only offspring that was grossly deformed was a low dose pup with a vestigial tail.

Effects possibly due to F were increased neonatal deaths at the top dose & depressed growth of nurslings at upper two levels.

2) Fertility study #2. In an i.v. fertility study conducted by IRDC, groups of 25 M & 25 F Charles River rats were injected once daily for 60 days before & through mating for the males & for 14 days before mating & up to day 7 of gestation for females with 0, 30, 100, and 200 mg/kg. Offspring were delivered surgically on day 20 & examined for gross, visceral, & skeletal defects.

Results

Male & female fertility as well as in utero development of offspring were unaffected at all test levels. There was no indication of teratogenicity.

The only signs of toxicity were 5 male deaths at the mid dose and 8 males and 1 female at the top dose, all temporally associated with injection. Males seemed to be more sensitive to the drug. Finally, post-dose tachycardia was present in high dose males. Growth of males & females was reduced slightly at the higher levels.

3) Teratology Studies in Rats:

a) In a preliminary dose-range study (#80103) conducted by Y, groups of 12 pregnant C-R rats were dosed orally by catheter with 0, 500, 1000, or 2000 mg/kg of F during days 7 17 of gestation. One half of the animals were delivered surgically on day 20 and the remainder were allowed to deliver naturally.

Results

In this dose range-finding study, F was essentially without effect. The only questionable findings were in the group that delivered naturally & included slight increase in length of gestation at the low & high doses, slight reduction in live birth rate and delivery rate at the top dose. Since the number of animals used per group was small, and since the results in the caesarian group were normal, the few disturbances seen in the group that delivered naturally may not be drug related.

b) In an i.v. Teratology Study conducted by Yamanouchi groups of 30-37 pregnant C-R rats were injected i.v. with a 2% sol. of F at doses of 0, 30, 100, and 200 mg/kg during days 7-17 of gestation. Two thirds of the dams were delivered surgically on day 20 and the remainder were allowed to deliver naturally. The F1 offspring were examined for gross, visceral, and skeletal defects & those delivered naturally were allowed to reproduce.

Results

F caused clinical reactions at 10 and 200 mg/kg (ataxia, piloerection, reduction in motor activity, bradypnea, prostration) associated with injection. Three of 37 dams died at the top dose. Reproductive parameters were essentially undisturbed by all test doses of F. The only suggestions of reproductive impairment were slightly impaired growth of the male & female F1 offspring at the top dose, and slight reduction in the fertility of the F1 high dose animals. There was no evidence of teratogenicity (rate of terata low & comparable in all groups).

4) Teratology Studies in Rabbits:

a) Dose range-finding study by Yamanouchi in non-pregnant rabbits: Groups of five N.Z. White rabbits were gavaged once daily with 0, 500, or 2000 mg/kg of F for 14 days.

Results:

All rabbits survived but both dosages produced distinct toxicity, e.g. growth depression at the low dose & weight loss at the top dose, corresponding reductions in food consumption and dose related reductions in the absolute and relative weight of the liver. There were no clinical reactions & necropsy resealed no gross abnormalities of the thoracic and abdominal organs.

b) Dose range-finding study in pregnant Rabbits:

In the first study (#80106), groups of 8 pregnant N.Z. white rabbits were intubated once per day with 0, 200, 500, 1000, or 2000 mg/kg of F during days 6 to 18 of gestation.

In a second study (# 80111), groups of 5-8 pregnant N.Z. White rabbits were intubated with 0, 50, 100, or 200 mg/kg of MK-208 during days 6-18 of gestation. In both studies, animals were sacrificed on day 29.

Results

In the first study, F exerted toxic effects at all levels. This included abortions in 2/7 at 200 mg/kg, 4/6 at 1000 mg/kg, and 3/6 at the top dose. These abortions occurred six to eleven days after cessation of treatment on day 18 of gestation. Growth was depressed in a dose related way at all levels; growth was depressed during time of drug administration (days 6-18 of gestation), but continued to deteriorate after cessation of drug administration (days 18-29 of gestation). The dams experienced a mean weight loss at all dose levels.

Food consumption was depressed at all drug levels in a dose related way, more so after the period of drug administration. Necropsy revealed yellowish-brown livers in 3 dams at 200 mg/kg and 1 case each at the other drug levels.

There was a dose related reduction in the weight of the fetuses and of the placentae. There was also an increase in dead fetuses in the test groups. Gross anomalies were present in 1 each at the 2000 mg/kg and 1000 mg/kg (in each case included flexion of the left fore-limb) and in 6 from one litter at 500 mg/kg level (2 general edema & 4 edema of head region). Skeletal variants were absent but visceral anomalies included 2 cases of gall bladder defect at 200 mg/kg & one at 1000 mg/kg and one case of bifurcation of the cardiac apex at 2000 mg/kg.

In the second study, growth and food consumption were essentially unaffected up to 100 mg/kg; at 200 mg/kg, growth was depressed slightly.

No drug related deaths or abortions occurred. Whereas none of the 58 control fetuses showed anomalies, three of 46 high dose pups showed anomolies exencephaly, cleft palate, open eyelids & cataract in one, agenesis of the gall bladder with or without rib bifurcation in 2 others).

c) Rabbit Teratology Study (# 81101) by Yamanouchi)

Groups of 9-14 pregnant N.Z. white rabbits were intubated daily during day 6-18 of gestation with 0, 30, 200, or 300 mg/kg and sacrificed on day 29. Offspring were examined for external, visceral, and skeletal defects.

Results

The doses of 30 and 200 mg/kg were essentially without adverse effect. The only disturbances possibly related to drug administration were a transient mild depression of body growth at the beginning of drug treatment at 30 & 200 mg/kg, a slight increase in percent stillbirths at same (12 and 9% at L & M vs 7% in controls), and a reduction in the percent of lumbar ribs (28% vs 43% in controls). One mid dose mother aborted following severe anorexia & weight loss but this dam also showed evidence of accidental intubation at necropsy. The top dose was clearly toxic, causing severe anorexia & growth depression, 4 abortions (3 of which followed severe anorexia & weight loss), a distinct increase in stillbirths (16% vs 7% in controls) with a corresponding slight reduction in avg. live litter size, yellowish liver (fatty metamorphosis) most likely secondary to starvation in five dams. There were no external anomalies at any dose, but 2/77 pups at the high dose showed bent ribs and there was a decrease in the number of lumbar ribs in offspring from the upper two levels as well as a decrease in number of sacrocaudal vertebrae at the high dose. The latter variations reflect delayed ossification and are likely secondary to poor nutrition. The anorexia & weight loss which appeared during treatment with 500 mg/kg of F persisted and in some cases intensified after cessation of drug treatment on day 18 of gestation. All of the four abortions at the top dose occurred after discontinuation of drug treatment and in 3/4 cases was related with severe growth depression.

d) Intravenous dose range-finding studies in rabbits:

In three non pregnant rabbits, an acute I.V. dose of 100 mg/kg was non-lethal, but 200 mg/kg killed 1/3 and 400 mg/kg killed 2/2.

A study conducted by Yamanouchi utilized 2 groups of 3 pregnant N.Z. White rabbits injected I.V. with 50 or 200 mg/kg of F during days 6-18 of gestation. Reproduction was not drastically impaired, but one dam injected with 50 mg/kg aborted on day 27 and one pup from the top dose showed fusion of the 2nd and 3rd vertebrae. Clinical reactions, e.g. decreased activity & decreased muscle tonus occurred at the top dose only.

e) Intravenous Teratology Study in Rabbits (Study #81107 by Yamanouchi).

Groups of 13-14 pregnant N.Z. White rabbits were injected I.V. during days 6-18 of gestation with 0, 10, 30, or 100 mg/kg of F. After sacrifice on day 29, offspring were examined for external, visceral, and skeletal defects.

Results

None of the test doses produced significant disturbances of reproduction. But growth was somewhat depressed (no weight gain) at the low & mid doses and the percent of empty implantation sites was increased at the same doses. Two abortions occurred at the low dose to dams that showed only mild growth depression. The absence of a dose related relationship raises some doubt whether the aforementioned effects were causally related to the drug.

There was no clear evidence of teratogenicity; isolated anomalies observed in offspring of the test groups were retroesophageal right subclavian artery in one low dose pup, fusion of the 1st & 2nd thoracic vertebra & fusion of the 1st & 2nd rib in one low dose pup, fusion of 7th cervical vertebra and 1st thoracic vertebra with associated vertebrae body defects in a third low dose pup, and finally abnormalities of the thoracic vertebra & ribs in a high dose pup. These effects were not seen in controls.

f) Effect of oral and I.V. administration of F on food consumption in pregnant rabbits: In this study conducted by Yamanouchi, eleven N.Z. White rabbits were gavaged once daily with 500 mg/kg of F during day 6-18 of gestation and allowed to deliver naturally. After a suitable recovery period, the surviving dams were mated again and the six found pregnant were injected I.V. with 100 mg/kg during days 6-18 of gestation.

Results

In the oral phase, F quickly produced a state of total & persistent anorexia in 5/11 dams with an accompanying significant loss in body weight. Appetite & growth was not affected in the other animals. Between days 20 and 27 of gestation (after drug administration had terminated and while animals were still anorexic) the five dams showing appetite & growth suppression aborted. None of the other dams aborted.

In the I.V. study, no growth or appetite suppression was induced & no abortions occurred. The only fetus malformed was one showing exencephaly from a mother injected with 100 mg/kg I.V.

g) Plasma levels in pregnant rabbits

These groups of 5 pregnant N.Z. White rabbits were treated orally with 30, 200, and 500 mg/kg of F during days 6-18 of gestation. Plasma levels were determined at 2 hrs post drug on days 6, 12, & 18 of gestation and at hrs 6 & 24 on day 18.

Results

F produced a predictable depression of appetite & growth. Plasma levels were increased in a dose related manner at 2 hrs post drug at all times tested. However, they were substantially elevated at 24 hrs post drug only at the 500 mg/kg level, which is the threshold level for inducing abortions orally.

5. Peri - and Post - Natal Studies

a) Groups of 25 female rats were dosed orally from day 15 of gestation to the 21st day of weaning with 0, 100, 500, and 2,000 mg/kg of F. Growth, development, & fertility of the F_1 generation was assessed as well as effects on the F_2 generation.

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4) Reversion Test of purified & crude preparations of C-nitroso-F: Neither the purified nor crude nitrosamine forms of F were mutagenic, with or without metabolic activation, against various strains in the Ames test.

5) Repair Test:

F and cimetidine did not inhibit growth of B. subtili strains M45 and H_{17} up to 10 mg/plate, but tiotidine did slightly at the higher concentrations.

6) Repair Test of F, Cimetidine, & Tiotidine after reaction with nitrite:

After reaction with nitrite, both F & Tiotidine were highly positive (growth suppressing) against B - subtilis strains M45 and H_{17}. Each drug suppressed growth of the recombination repair deficient strain M45 much more than the wild strain H_{17}

7) Repair Test of pure & crude C-nitoso - F

Both forms suppressed M45 & H_{17} at the high concentration of 7320 microgram/plate but supression of M45 was not sufficient to reflect a mutagenic activity.

8) Micronucleus Test in Mice

Mice were treated orally for two days with 0.5, 1, and 2 g/kg, then sacrificed for examination of bone marrow cells. F did not cause chromosomal aberrations judged from the no. of polychromatic RBC's with micronuclei.

9) Mammalian Cell Mutagenesis Assay in chinese hamster lung fibroblasts:

In two separate tests, with or without metabolic activation, F did not induce mutation of Chinese hamster lung fibroblasts in vitro up to a conc. of 10 mM per plate whereas positive controls were active.

10) Mammalian Cell Mutagenesis Assay in Ovary cells:

In two separate assays, with or without metabolic activation, F did not induce mutation of Chinese Hamster ovary cells in vitro up to 3mM/plate whereas positive controls were active.

11) Chromosome Aberration Test in Mice.

Groups of 5 mice were treated orally with acute or subacute (5 days) doses of 50, 100, or 200 mg/kg of F I.V. Twenty four hrs. after the last dose, bone marrow cells were examined for chromosomal abberations. The cells from mice treated acutely or subacutely did not show evidence of significantly increased chromosomal aberrations up to the maximum dose.

F) Special Studies

1) Effect on thyroid:

F administered for 5 wks to groups of 15 male rats at 0, 400, 1000, and 2000 mg/kg, did not affect serum level of thyroid hormones, nor the weight or histology of the thyroid gland.

2) Immunogenicity in mice:

F either alone or complexed to a carrier protein, was injected i.p. into mice. Following injection, no IgE antibody appeared up to 25 days after injection, however the positive control, DNF complexed to protein, produced obvious IgE titers.

3) Immunogenicity in G pigs

Groups of 8 g - pigs were injected s.c. three times at six day intervals with 1 or 10 mg/kg of F. Fourteen days after the last injection, the animals were challenged I.V. with F. No F treated died or showed anaphylactic reactions whereas 3/8 positive controls died.

4) Rabbit Eye Irritation:

Instillation of solutions of F up to 1% and at pH 5.5 caused no irritation to the eye or conjunctiva of rabbits.

5) Rabbit Muscle Irritation:

0.1 ml of 0.001% solution of F in distilled water caused no more irritation than saline & was much less irritating than the same volume of 0.75% acetic acid when injected one time into the vastus lateralis muscle of rabbits.

6) In vitro Hemolysis Test:

The injectable formulation (20 mg of F, 8 mg of L-aspastic acid, 40 mg of D-mannitol dissolved in 2 ml of distilled H_2O) caused no hemolysis in vitro in human or rabbit blood. Likewise, no hemolysis or precipitation resulted when two samples of same were tested on washed human RBCs.

7) Irritation in Dogs:

When the above injectable formulation was administered i.m., I.V., intraarterially, or perivenously to dogs at a dose of 2 ml (containing 20mg of F)one time at separate sites, no undue irritation was observed macroscopically or histologically at 24, 48, or 46 hrs. post-drug. Irritation at each test site was comparable to corresponding saline controls.

8) Infusion Study in dogs:

Groups of 3-4M & 3-4 F beagles were infused I.V. 6 hrs per day for 7 days with a 0.4% injectable formulation of F at doses of 0, 4, 12, & 36 ml/kg/day (equivalent to 0, 16, 48, and 144 mg/kg/day).

Results:

No dogs died ? injection sites were not affected. The only indication of toxicity was emesis, hypoglycemia, and slight hypotension at the high dose only.

9) Skin Sensitization in G. Pigs:

Topical application of the injectable formulation of F did not elicit a sensitization reaction in the skin of G Pigs which had been previously treated intradermally & topically with the drug. This model reacted very positively to penicillin.

6) Pharmacology

1) In vitro histamine H_2 receptor antagonism:

In vitro, F inhibited histamine induced tachycardia of the isolated rt. heart of G. Pigs as well as histamine induced relaxation of the isolated rat uterus, showing 10 & 166 times the activity of C respectively. F also inhibited dimaprit induced tachycardia of the isolated G. Pig heart in a non-competitive unsurmountable way (unlike C & R which showed competitive surmountable antagonism). In the latter, F was bound rather tightly to the H_2 receptor in contrast to R and C which are removed easily through washing.

F inhibited histamine sensitive adenylate cyclase (and thus cyclic AMP formation) in membrane fragments of g. pig gastric mucosa and hippocampal homogenates of g. pig brain. It displayed a dose related competitive antagonism qualitatively similar but 24 times greater than that shown by C.

Like R, F inhibited in a competitive way the utilization of aminopyrine in isolated gastric glands of rabbits. This response reflected inhibition of gastric secretion.

Finally, F competitively and reversibly inhibited dimaprit induced relaxation of isoproterenol stimulated contraction of isolated g. pig lung strips.

F showed in vitro a lack of effect on responses mediated by H_1 - histamine, beta-adrenergic and muscarinic receptors, or acetylcholine release. It was also inactive in radioligand binding tests relating to dopaminergic, neuroleptic, serotoninergic, adrenergic, cholinergic and purinergic sites.

2. <u>In vivo Antisecretory Activity</u>:

F inhibited gastric secretion in gastric fistula dogs stimulated with either histamine, gastrin, 2-deoxy-D-glucose as well as food and dimaprit in Heidenhain pouch dogs. Activity was seen by both the I.V. and oral routes. The effect was characterized by a reduction in volume and in acid & pepsin output and to a lesser extent in acid concentration of gastric secretions. Comparative evaluations invariably showed F to be most potent by far, R intermediate, and C the least potent; against histamine stimulation in orally treated dogs, the most sensitive species tested, F was 95 times more active than C & 14 times more active than R on a weight basis & 127 & 15 times as active respectively on a molar basis. The oral and I.V. ED50 of F against histamine evoked gastric secretion in dogs was only 0.03 mg/kg in each case as compared to 2.86 mg/kg & 1.84 mg/kg respectively for C.

The time course of gastric antisecretory effect of F appeared to be somewhat longer than C or R. For example, when single equivalent antisecretory doses of F and R were given orally to histamine stimulated dogs, F exhibited 67% inhibition 24 hours post drug administration vs. only 2% for R. By the I.V. route however, duration of activity of F against a constant stimulatory dose of histamine in dogs was only slightly longer (1.3) than C.

In Heidenkain (vagally innervated) pouch dogs, F and C both competitively inhibited the secretory response of dimaprit, a specific H2 receptor aganist, whereas both induced an unsuromountable and thus non-completitive antagonism of methacholine and pentagastion.

In gastric fistula cats, F, given s.c., was 38 and 5 times more antisecretory than C and R against histamine and 20 and 8 times against tetragastrin.

In chronic fistula rats, F and C inhibited basal acid output mainly by decreasing acid concentration; both also lowered pepsin output to a lesser extent. F was about 15 times more potent than C. In pylorus ligated rats treated orally, intraduodenally, and I.V., the ED50 antisecretory dose was similar and averaged 0.58 mg/kg.

No tolerance to the gastric antisecretory effect of F was seen in rats and dogs treated orally with subacute doses.

In rats treated p.o. with 3 mg/kg of F for 8 days, and "acid rebound" effect was noted 3 days after stop of treatment. In another study however, this rebound effect did not appear 1 or 3 days after repeated oral dosing of rats with 5 mg/kg b.i.d. for 30 days.

F inhibited cyclic AMP formation in the gastric mucosa of untreated and histamine stimulated rats, but mostly of the latter.

3) Antiulcer Activity;

F inhibited gastric ulcers induced in rats by a variety of agents or procedures (histamine, indomethacin, aspirin, cysteamine, stress, pyloric ligation) as well as or against duodenal ulcers induced with mepirizole. the ED50 of F ranged from 0.17mg/kg to 0.6 mg/kg and potency ranged from 17-44 times that of C. Effectiveness of F was greatest against histamine induced ulcers. Antacid (maolox) enhanced the antiulcer activity of F in rats.

4. Effect on serum gastrin:

In rats in which the acidity of the stomach was maintained through perfusion of HCl, F did not elevate serum gastrin whereas C did at equivalent antisecretory doses. No data are available on serum gastrin levels in animals treated with F alone.

5) Miscellaneous G. I. Effects:

In normal rats, F did not affect the histamine content of the gastric mucosa, but it did lower the mucosal level of endogenous PGE_2 and PGI_2 to a slight extent; C however lowered these prostaglandins to an even greater extent.

F did not influence propulsion of a charcoal meal in mice but it shortened gastric residence time in rats and dogs. In cats, F did not prevent the fall of transgastric electropotential difference which accompanies the administration of aspirin and which is considered to reflect disruption of the gastric mucosal barrier.

6. Cardiovascular Activity:

F exerted no effect on blood pressure, ECG, or respiratory rate in conscious dogs up to 30 mg/kg p.o. In the general toxicity studies conducted in dogs, no ECG or heart rate changes were noted in dogs treated orally with up to 2000 mg/kg b.i.d. for 30 days, up to 1000 mg/kg for 13 weeks, or 500 mg/kg for one year.

In spontaneously hypertensive rats, F had no effect on blood pressure at 10 mg/kg p.o.

Dogs injected I.V. with 1 mg/kg acutely displayed no effect on ECG or heart rate. However 10 mg/kg I.V. caused slight tachycardia and hypotension, and 30 mg/kg caused distinct tachycardia, hypotension, T wave elevation and increased respiration. The I.V. injection of 300 mg/kg acutely induced respiratory arrest, pronounced sustained hypotension, and finally death 20 minutes post drug.

F exerted no effect on the rate or contractility of the isolated G. Pig atrium.

In a six month I.V. toxicity study in dogs at 5, 25, and 100 mg/kg, reddening of mucous membranes possibly due to vasodilatation and significant tachycardia was noted at 100 mg/kg slight tachycardia only at 25 mg/kg, but no cardiovascular effects at 5 mg/kg.

7. Autonomic Reactivity:

Three mg/kg I.V. of F displayed no effect on muscarinic, nicotinic, histaminergic, H, or sympathetic alpha or beta receptors in dogs. It counteracted dimaprit induced hypotension in dogs through H_2 receptor antagonism.

8. CNS and Behavioral Effects:

F did not elicit any oral CNS effects at high oral doses (up to 2000 mg/kg b.i.d.) in mice, rats, rabbits, cats, or dogs other than retching or vomiting in dogs. It had no effect on locomotion or rotarod performance in mice treated with 100 mg/kg p.o., although 100 mg/kg I.V. reduced activity slightly in this species. Further, F had no effect on thiopental induced sleeping time in mice or hexobarbital induced sleeping time in rats up to 100 mg/kg p.o. or I.V. whereas C prolonged sleeping time.

F had no effect on pentetrazole induced seizure in mice, displayed no non-narcotic analgesia in mice, nor interfered with morphine analgesia.

Doses of up to 10 gm/kg p.o. or 30 mg/kg I.V. had no visible effect on behavior in mice and rats. Further, F had no effect on metamphetamine induced stereotyped behavior in rats while C did have an effect. Condition avoidance behavior in rats was unaffected with up to 100 mg/kg p.o. but it was slightly impaired in squirrel monkeys at 3 and 9 mg/kg p.o. F exerted no EEG effects in immobilized cats up to 10 mg/kg p.o. Hippocampal after discharge in rabbits was unaffected up to 10 mg/kg I.V. or in cats up to 3 mg/kg I.V., but was delayed significantly in latter at 10 mg/kg. In cats injected I.V. with 3 mg/kg of F, % of the plasma concentration of drug was detected in cerebrospinal fluid. In dogs, a dose of 100 mg/kg I.V. elicited vomiting which was not preventable by metoclopramide.

9. Drug Interaction

In Vitro:

F and R demonstrated significantly less binding to Cytochrome P450 than C. In keeping with this, F and R did not display unusual U.V. spectra with microsomal preparations from uninduced and phenobarbital induced rats whereas, C did. Further, F and R had little effect on in vitro cytochrome P450 activity or Benzphetamine N-Demethylase activity with untreated or phenobarbital stimulated microsomes, whereas, C did. F and R had virtually no effect on the in vitro activity of microsomal 7-ethoxycoumarin O-Deethyliase activity with untreated phenobarbital, or 3 MC induced microsomes, whereas C did. F and R did not suppress 16 alpha, 7 alpha, and 6 beta hydroxylases of testosterone in liver microsomes of mice, whereas C did. Finally, F did not inhibit amenophyrine N-demethylase activity and diazepam metabolism in vitro, whereas C did.

In Vivo:

F did not delay the metabolism and excretion of diazepam, warfarin or propranolol in dogs, whereas C did judging from increased half-life, higher peak plasma concentrations, and greater AUC's of these drugs.

F and R did not increase the plasma concentration of antipyrine in rats, whereas C did significantly.

Sleeping time of pentobarbital was unchanged in rats pretreated with F for 14 consecutive days, but significantly reduced in rats pretreated with phenobarbital, a hepatic enzyme inducer. In addition, the phenobarbital-treated rats excreted more ascorbic acid in the urine and displayed larger livers than the F treated rats.

F did not affect hexobarbital sleeping time in rats, whereas C did so significantly.

10. Anti-androgenicity:

Castrated rats supported with exogenous testosterone showed no reduction in prostate or seminal vesicle weight when treated with 50 mg/kg p.o. of F for 7 days. The same model however showed significant reduction in the weight of these organs when treated with the same dose of C.

F did not inhibit in vitro the binding of testosterone to the androgen receptr present in the rat prostate cytosol.

11. ADME

a. Absorption

About 30-40% of an oral dose is absorbed in rats, dogs, and humans. In bile cannulated rats, 28% of an oral dose was recovered in the urine, 2.4% in the bile, and 70% in the feces. Hence, the bioavailability of F is moderate.

The bioavailability of type A crystals present in bulk material was essentially the same as type B crystals (presumably the early pilot batches).

In vitro, 21 to 27% of drug is bound to plasma protein in rat, dog, and human blood. In vivo, 15 to 22% of either F, C or R are bound to protein in the blood of human recipients.

In rats, the 1/2 life after oral dosing was 1.9 hour; peak plasma concentration was reached in about 2 hours.

In humans and dogs treated p.o. the half life was about 3 hours and the peak plasma concentration was reached in 3 hours.

Repeated p.o. or i.v. dosing of dogs showed no tendency for accumulation in the plasma.

b. Distribution:

In rats treated orally with a single dose, the levels of F were highest in the G.I. tract, kidneys, liver, submandibular glands, and pancreas in descending order. After i.v. administration the same order of distribution was found except that none was present in the G.I. tract. Little if any was found in the brain in either instance. All evidence of drug was absent by 24 hours post-drug.

Whole body radiographic studies of acutely-treated rats revealed only trace amounts after oral dosing (exclusive of the G.I. tract), but significant amounts in the liver, kidneys, G.I. tract, arteries, epiphyseal membranes, fasces, and uvea after i.v. dosing; drug disappeared in a short period of time and none was ever present in the brain or spinal cord.

Administration of drug p.o. or i.v. to pregnant rats showed only traces in fetal tissue, but significant amounts in the milk.

Multiple dose testing of rats for 21 days revealed slight rise in tissue levels of drug, but no significant accumulation; excretion pattern after 21 days (20% in urine and 70% in feces) was similar to that after acute dosing. Virtually no drug was detected in the brain.

Young rats injected i.m. with F from day 1 to day 28 of lactation showed relatively high levels of drug in tissues originally, brain included, but diminishing levels with time. Content of the brain was always less than that in other organs and nil after day 21. The descending order of distribution was kidney, liver, blood, heart and brain.

Young suckling rats nursing from mothers treated p.o. or i.v. on day 14 of lactation showed drug in liver and kidneys but none in the brain.

c. Metabolism:

Metabolism is very similar in rats, dogs and humans in that in each case 80% of absorbed drug is unmetabolized, the remaining 20% being metabolized to one specific product, the S-oxide. Almost all of the absorbed parent compound and its S-oxide derivative are excreted in the urine in each species. The structure of the S-oxide, which incidentally exhibits 1/270th the H_2 receptor antagonism of the parent, is as follows:

Famotidine S-oxide
(identical to F except for O attached to S atom)

the relative immunity of F to metabolism suggests that it will be virtually unaffected by hepatic first pass effect.

d. Excretion:

Excretion of F in rats, dogs, and humans is essentially the same. In each case virtually all of the absorbed drug is eliminated by the kidneys, a very small fraction being eliminated through the bile. This is true whether the drug is given p.o. or i.v.

12. Miscellaneous:

F had no effect on pancreatic or biliary secretion, hepatic blood flow, spontaneous G.I. motility, methacholine induced salivation, immediate hypersensitivity reactions, cellular or humoral immune responses or histamine induced asthma in guinea pigs.

Evaluation:

Famotidine (F), which is structurally related to tiotidine has been clearly shown from pharmacological assays in vitro and in animals to be a very potent and very selective H_2 receptor antagonist and gastric antisecretory agent. Less certain is that the drug acts on the gastric H_2 receptor in a competitive way like cimetidine (C) and that it is somewhat longer acting in vivo.

In all of the assays, in vitro and in vivo, and regardless of route (p.o. or i.v.) or the secretory stimulant, F was invariably many times more potent than cimetidine(C) or ranitidine (R). For example, against histamine induced gastric secretion in dogs, orally administered F was 95 and 15 time more effective than C and R respectively. The single oral antisecretory ED50 dose of F in the latter model was only 0.03 mg/kg, which is 1/33 the human dose.

The nature of the antagonism was competitive against some H_2 receptors, non-competitive against others. For example, in assays involving gastric receptors (inhibition of dimaprit induced gastric secretion in Heidenhain pouch dogs, inhibition of adenylate cyclase activity and cyclic AMP formation in membrane fragments of guinea pig gastric mucosa), F displayed competitive inhibition qualitatively like that shown by C. However, in an assay that involved non-gastric H_2 receptors (inhibition of dimaprit induced tachycardia of the isolated guinea pig heart), F showed distinct non-competitive and unsurmountable antagonism, whereas C and R showed competitive easily reversible antagonism. In addition, F was shown to be tightly bound to the H_2 receptors in this model while C and R were loosely bound. Since F was always a competitive inhibitor in assays involving gastric systems, it is assumed that it will exert a competitive type antisecretory action in man similar to that observed with C.

The time course (duration) of gastric antisecretory activity of F was somewhat longer than R and C. For example, 24 hours after the oral administration of equivalent antisecretory doses of F and R to histamine stimulated dogs, 67% inhibition still remained with F, but only 2% with R. However, by the i.v. route in histamine stimulated dogs, the duration of antisecretory effect of F was only 1.3 times longer than C. It would appear then that F will be somewhat longer acting than R or C, but not extraordinarily so like omeprazole; 24 hour achlorhydria resulting from a single dose of F is quite unlikely despite the drug's remarkable potency.

The selectivity displayed by F was truly outstanding; whereas, only 0.03 mg/kg was required to demonstrate significant inhibition of gastric acid secretion in histamine stimulated dogs, hundreds times that dose showed no properties indicative of an H_1 receptor antagonist (conventional antihistamine), an anticholinergic or cholinergic, a histaminergic, an alpha- or beta-agonist or antagonist, a CNS stimulant or depressant, a tranquilizer, a behavior altering agent, or an allergenic compound. No cardiovascular or ECG effects were apparent in dogs after an oral dose of 30 mg/kg (1000 times ED_{50}).

Most incredible was the total absence of overt clinical reactions or serious toxicity in rats and dogs treated orally by gavage for 4 to 13 weeks with up to 2000 mg/kg b.i.d., a level which exceeds the ED50 in dogs by a factor of 133,333!

Based on the preclinical findings, F will quite likely be devoid of anti-androgenic properties and not be prone to serious drug interaction problems. For example, like R, and unlike C, F did not bind significantly to cytochrome P450 enzymes of the liver in vitro and did not alter the pharmacologic activity, metabolism, or excretion of a number of C sensitive drugs (diazepam, warfarin, propranolol, pentobarbital, hexobarbital and antipyrine). Concerning anti-androgenicity, F did not influence the effect of exogenous testosterone in castrated rats, interfere with the in vitro binding of testosterone to androgen receptors, or reduce prostate or seminal vesicle weights in rats or dogs treated subacutely with up to 2000 mg/kg b.i.d.

We have no information in animals whether F elevates serum gastrin through induction of gastric hypoacidity. All that has been shown is that F does not increase serum gastrin in rats in which gastric acidity is kept normal by acid perfusion; this contrasts with C which raises serum gastrin under the same conditions.

One striking feature of the pharmakinetics of F is the almost identical way rats, dogs, and humans handle the drug. In all three species, F is moderately absorbed (30-40% of dose) is 20% bound to plasma protein, achieves peak plasma concentration in 2-3 hours, is slightly metabolized to just one metabolite, the S-oxide of the parent compound, and is almost all exereted via the kidneys (98% of absorbed drug via kidneys 2% via bile). This suggests that the pharmacological and toxicological results in animals are probably reasonably reflective of the drug's clinical potential.

The distribution studies showed the customary high concentrations in the kidneys and liver and negligible amounts in the brain and fetal tissue, but one peculiarity was the finding of high amounts of drug in the milk of lactating rats. This may explain why the growth of their nursing offspring tends to be depressed. Another noteworthy finding was the demonstration that, in newborn rats injected i.m. daily for 28 days, F passes the blood-brain barrier with decreasing efficiency until the 21st day, after which time no drug passes the barrier.

Concerning toxicity, the Yamanouchi Company and MSD have together supplied a wealth of animal toxicity data: acute studies in two species by all routes, numerous subacute, chronic, and reproduction tests by the oral route, oral carcinogenicity studies in mice and rats and a large battery of various mutagenicity assays.

As a whole, these data show F to be an astonishingly non-toxic and paradoxically inert compound, especially when one considers its extraordinary antisecretory potency (oral gastric anti-secretory ED50 in dogs is just 0.03 mg/kg and the daily human dose is only 1 mg/kg). For example, the acute oral LD50 of F in mice and rats was in the order of 4000 mg/kg when given in solution form and 8000 mg/kg in suspension form. In multiple dose studies, rats tolerated as much as 2000 mg/kg b.i.d. for 13 weeks and 1000 mg/kg for one year while dogs tolerated as much as 2000 mg/kg b.i.d. for 30 days and 500 mg/kg for one year. In these studies with doses far in excess of the HD, F appeared to be a rather inert compound in that it elicited no overt clinical reactions and no dramatic disturbances. The only indications of drug toxicity were proteinuria in rats and dogs at high doses, occasional elevations of SGPT in dogs, and alteration of chief cells, enlargement of the nuclei of these cells, and finally an increase in eosinophilic cytoplasmic granularity (ECG) of these pepsin secreting cells. Examination with electron microscope revealed only an increase in the density of these granules over that seen in the untreated animal. The threshold dose for this effect appeared to be about 2000 mg/kg p.o. and it was completely reversible within 16 weeks upon discontinuation of treatment. The sponsor conjectures that these chief cell changes may reflect reduced turnover of pepsinogen secondary to the drug's antisecretory effect, but this is difficult to reconcile with the observation that the drug still elicited these changes in rats subjected to continuous HCl perfusion of the stomach. However, the changes did not involve a change in the intracellular concentration of pepsinogen or ability of the cell to secrete pepsin.

One effect that was surprisingly absent in all of the animal studies was ECL cell hyperplasia in the gastric fundus. This gastrin dependent effect is characteristically seen in animals, especially rats, with potent long-acting gastric antisecretory agents (omeprazole, SKF-93479, Loxtidine, and BL-6341A). Perhaps F did not produce ECL cell hyperplasia because, despite its extraordinary potency and somewhat greater duration of action, its time course of antisecretory effect is still incapable of inducing sustained (24 hr.) achlorhydria and hypergastrinemia or anything comparable to it. This of course is a favorable finding because it tends to rule out a potential for inducing gastric carcinoid tumors which arise from hyperplastic ECL cells.

The various mutagenicity tests conducted on F showed it to be lacking in mutation potential. Following reaction with nitrite however, the reaction product (which likely included nitrosamines) was mutagenic against B subtilis strains M45 and H17.

The significance of the latter finding is doubtful however, since F was completely without carcinogenic potential in an oral carcinogenicity study of 92 weeks in mice and 106 weeks in rats up to 2000mg/kg/day in each case. Specifically, there was no evidence of gastric mucosal metaplasia, dysplasia, or neoplasia; there was no sign of the adenocarcinomas which appeared in the pylorus of rats treated for 6 months or more with structurally related tiotidine; nor was there any mention of ECL cell hyperplasia or carcinoid tumors in the gastric fundus. Finally, no carcinogenicity was suggested in any other organ, testes and liver included.

The reproduction studies conducted in animals provided essentially favorable results. Disturbances of reproductive parameters occurred only at high levels and appeared to be related to the sustained appetite suppressant properties of the drug. For example, the drug induced significant anorexia and sustained growth depression in pregnant rabbits at 200 mg/kg p.o. and above (but not at 100 mg/kg, 100 times HD). Some of the mothers that showed significant growth suppression at 200 mg/kg or above aborted their young and showed yellow livers at necropsy; also, the offspring of dams that did not abort gave birth to offspring that weighed less than corresponding controls. These effects, particularly the abortions, are no doubt indirectly due to prolonged starvation and not directly due to the drug. Supporting this is the fact that abortion never occurred during the drug treatment period, but later, (in the interval that separated termination of drug treatment and planned time of sacrifice of the mothers), and after virtual total anorexia had been in effect for some time. Also, abortion rarely occurred in a rabbit that did not show significant growth suppression.

Another disturbance possibly related to anorexia was the extended impaired growth of nursing neonatal rats. As suggested earlier, this may be attributed to the demonstration that F passes the blood-mamary gland barrier with ease in this species and accumulates in the milk and in addition passes the blood-brain barrier of neonates with relative ease for the 1st 21 days. The threshold maternal dose for neonatal growth depression was about 500 mg/kg. The persistence of the anorexia associated with F was reflected by the fact that weaned offspring continued to show growth depression for some eight weeks after separation from treated mothers.

In summary, based on the animal findings, Famotidine is predicted to be a very potent, very selective, long-acting and competitive H_2 receptor antagonist. The data also predict an unusually safe compound with a therapeutic index superior to cimetidine or ranitidine. It will likely compare to ranitidine and contrast with cimetidine in being devoid of anti-androgenicity and significant drug interaction complications. It should be like cimetidine and ranitidine and unlike metiamide in lacking a significant potential for agranulocytosis. Freedom from cardiovascular complications with oral use may be a unique advantage for F. Despite its extraordinary potency and somewhat longer duration of action, Famotidine does not seem to have any potential to cause sustained gastric achlorhydria, sustained hypergastrinemia, gastric ECL hyperplasia, or gastric carcinoids when administered once a day regardless of dose. In oral carcinogenicity studies of approximately 2 years duration in mice and rats up to 2000 mg/kg, (2000 times HD), it demonstrated no carcinogenic potential in any organ, the stomach, liver, and testes included.

In conclusion, Famotidine has been thoroughly investigated in animals and has clearly demonstrated efficacy and reasonable safety. Accordingly, this well-organized and very readable NDA (#19-462)by Merck Sharpe and Dohme for Pepcid(famotidine) Tablets is approvable from the preclinical standpoint.

The only recommendations offered are that the labeling:

1. warn against use by nursing mothers since in rats Famotidine accumulates in the milk, penetrates the blood-brain barrier of neonates with relative ease, and causes extended growth depression in nursing offspring.

2. suggest lowering of dose in patients with impaired kidney function since in rats, dogs and humans, absorbed drug is eliminated almost exclusively in the urine.

Pierre Deslauriers

Pierre Deslauriers, Pharmacologist

cc: Orig. NDA 19-462
HFN-110
HFN-110/CSO
HFN-110/PDeslauriers
HFN-102/VCGlocklin
HFN-345/GWJames
r/d init. PJDeslauriers,Act.Superv.Pharm.
cb:kg:rq:0705v:1-8-86
HFN-110 Dr Bachrach
HFN-110 Dr Stern

NOV 1 1984

[redacted]

September 13, 1984

Review and Evaluation of Animal Data
(Amendments of April 6, 1984)

The amendment supplies the following additional animal date:

1. Three month range-finding study in mice: Groups of 15 M and 15 F mice were gavaged once daily with MK-208 at levels of 0, 100-200, 400 700-1500, and 1000 mg/kg for 3 months in a study intended to find suitable doses for a carcinogenicity study.

   Results:

   Due to lack of toxicity, some dose levels were increased at five weeks. Viscosity limited the maximum dose to 2000 mg/kg. The drug was apparently very well tolerated at all levels, survival and growth being undisturbed. Necropsies were not done.

2. Ninety two week carcinogenicity study in mice: Groups of 50 M and 50 F Charles River mice were given MK-208 in suspension by gavage once daily at levels of 20, 200, and 2000 mg/kg/day (2000 times the daily human dose) for 92 weeks.

   Results:

   All treated groups performed as well as controls, the treated were like controls with respect to survival, growth, ophthalmoscopic exams, and gross and histologic findings except that diffuse distention of the glands of the fundus of the stomach was noted in 42% of the females at the top dose vs 11% among controls. There was no specific tumor that was statistically more prevalent in the test groups vs controls. There was no indication of carcinogenicity in either the stomach or testes. The only suspect finding was the occurrence of adenoma or adenocarcinoma of the lung in 31 of 100 low dose animals vs. 22/100 and 15/100 in the two control groups; however, the incidence at the mid and high dose was like the controls.

3. One hundred and six week carcinogenicity study in rats: Groups of 50 M and 50 F rats were gavaged with 20, 200, and 2000 mg/kg of MK-208 in suspension for 106 weeks. Two control groups each of similar number were used.

Results:

Again the test groups performed like controls. Morbidity among the males was slightly higher than controls at each test level and among the females as well at the top dose. For example, the percent of rats that died or were sacrificed before termination was 64%, 76%, 78% and 76% among the C,L,M, and H dose males and 42%, 48%, 52% and 72% among the respective females. Some of these deaths in the test groups were most likely due to accidental lung intubation considering the higher incidence of foreign body material in the lungs of animals at the upper two levels. Growth was unaffected and ophthalmoscopic exams were normal. Gross and histologic exams did not show carcinogenicity in any organ, the stomach and testes included. The only questionable finding was endometrial polyp in 3/50, 1/50, and 1/50 females at the high, mid, and low doses vs 0/100 control females, this tumor however was not statistically significant.
Non-neoplastic changes that were drug related included: glandular tissue distention in 5/50, 3/50, and 10/50 females from the low, mid and high dose levels vs 1/100 control females, nuclear enlargement of glandular mucosa in 9/100 and 26/100 from the mid and high doses vs 7/200 controls, eosinophilic cytoplasmic granularity of zymogen chief cells in 23/100 and 49/100 from the mid and high doses vs 25/200 controls. The sponsor considers all of the foregoing changes as "physiologic alterations related to the pharmacologic activity of the test article, i.e. inhibition of pepsin turnover secondary to inhibition of acid secretion".

EVALUATION:

The ninety two week carcinogenicity study in mice and the 106 week carcinogenicity study in rats did not show MK-208 to be carcinogenic in either species tested approximately two yrs. with daily dosages ranging up to 2000 mg/kg or 2000 times the human dose of 1mg/kg/day. It was notable that there was no evidence of carcinogenicity in either the stomach or testes.

Because some H2 receptor antagonists have produced stomach and testicular tumors near the end of a rodent's lifetime, it would have been preferable if these studies were lifespan studies. Since however they gave not even a suggestion of tumors in either organ after a fairly lengthy period of time (which extended over most of the animals' lifespan), the submitted studies appear to reasonably exclude the possibility of carcinogenicity.

Pierre Deslauriers

Pierre Deslauriers, Ph.D.

cc:Orig
HFN/110
HFN/110/CSO
HFN/110/PDeslauriers
cb/10/22/84/8628c
R/D: C.A.Resnick
Dr Bachrach
Dr. Stern

NDA
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Medical Officer's Review
NDA 19-462, Pepcid (famotidine)

Attachments: Package insert
Reprint of paper by Howard et al

12-31-85

New Drug Application NDA 19-462
Merck Sharp & Dohme Research Laboratories
Tablets PEPCID™ (Famotidine, MSD)

Item II - Summary of Application

A. Annotated Package Circular

HFN-110/CSO

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA 19-462

Name of Drug: Pepcid (famotidine)

Sponsor: Merck Sharp & Dohme Research Laboratories

Formulation: Tablets 20 mg and 40 mg.

Route of Administration: Oral

Proposed Clinical Use: Treatment of peptic ulcer disease.

Pharmacological Class: H_2-blocker.

Date of Submission: June 24, 1985

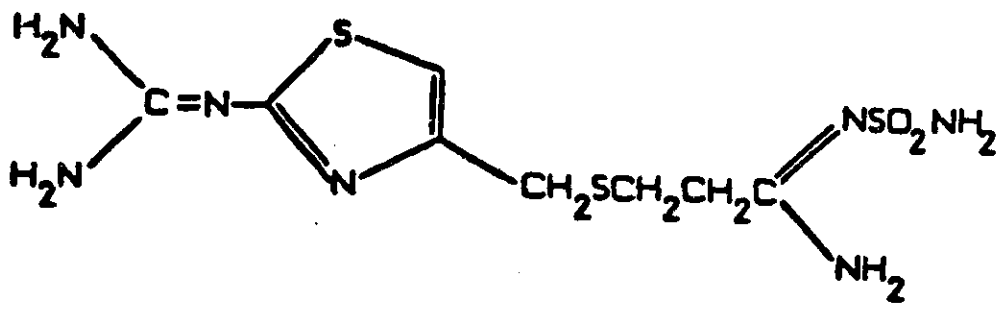
Material Submitted for Clinical Review:

Volume 1.1:	Summary of clinical reports
Volumes 1.27-1.38:	Full clinical reports
Volumes 1.49-1.53:	Case report forms on microfiche

Date Review Completed: 6 December 1985.

Reviewer: William H. Bachrach, M.D.

I. Background/Rationale: Famotidine, 3-[[[2-[(amino-iminomethyl) amino] 4-thiazolyl] methyl] thio]-M-(aminosulfonyl)-propanimidamide, with the following structural formula



is a long-acting H_2-blocker developed by Yamanouchi Pharmaceutical Company, Ltd., and licensed to Merck & Company, Inc. for distribution outside of Japan.

H_2-blockers inhibit gastric acid secretion and, primarily by this action, accelerate healing of peptic ulcers. Two H_2-blockers have been approved for marketing in the U.S., the first cimetidine, the second ranitidine. The use of H_2-blockers in patients with peptic ulcer disease has resulted in decreased patient morbidity and, according to some reports, in the need for elective operations, but the incidence of surgery for complications has not diminished.

Famotidine has been shown in animal and human studies to inhibit basal and stimulated gastric acid secretion. Based on these data, doses of famotidine have been selected for the evaluation of its effectiveness and safety in patients with peptic ulcer disease. Because of its long duration of action, it is expected that a once-a-day bedtime regimen will be effective.

No marketing experience is available because famotidine had not been marketed in any country at the time of submission of this NDA.

II. Clinical Pharmacology

A. Human tolerance

1. Japanese study

a. Title: An open study to assess safety, tolerability and drug levels in blood and urine of famotidine administered orally to normal male volunteers.

b. Investigators: T. Miwa, M.D. and M. Miwa, M.D., School of Medicine, Tokai University.

c. Design of study: doses of 5, 10, 20, 40, 80 and 160 mg were administered orally to each of 2 volunteers after the results of the preceding dose had been reviewed; 20 and 40 mg b.i.d. for 5 days were administered to 3 of the subjects after satisfactory completion of the single-dose sequence. The drug was administered on an empty stomach in the single-dose studies and 1/2 hour after meals in the repetitive dose study.

d. Results

(1) Safety: in none of the 12 volunteers were there any changes attributable to the drug in the vital signs, ECG, hemogram (including Coombs test), blood chemistry or urinalysis.

(2) Plasma concentration (figure 1): plasma levels, measurable with all except the 5 mg dose, were proportional to the size of the dose. Peak levels were reached between 2 and 3 hours. Drug levels were still detectible at 12 hours after doses of 40 mg and greater, but not at 24 hours at any of the single doses. No plasma accumulation of the drug was apparent in the multiple-dose studies.

(3) Urinary excretion (figure 2): the cumulative excretion of the drug amounted to 30-40% for all doses; most of the drug was excreted within the first 8 hours. After multiple dose administration, the daily excretion remained constant.

Figure 1
Bioavailability of Single Oral Doses

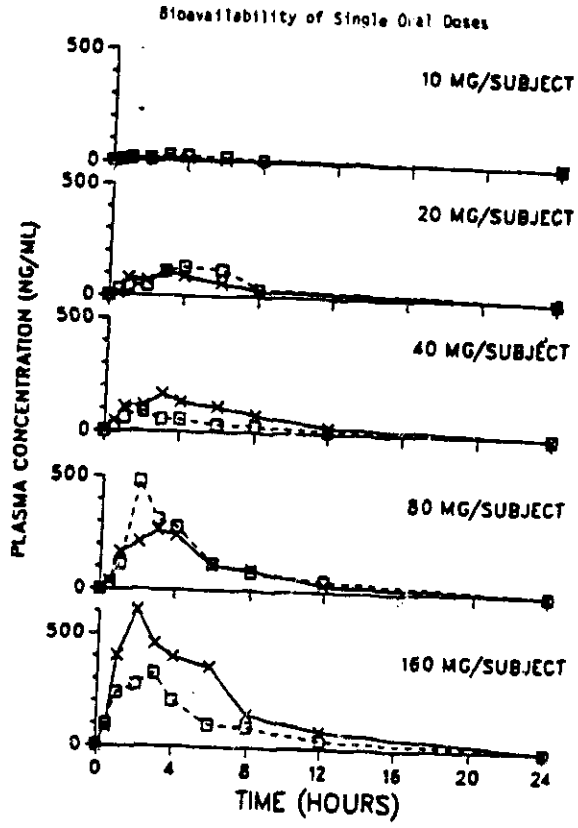
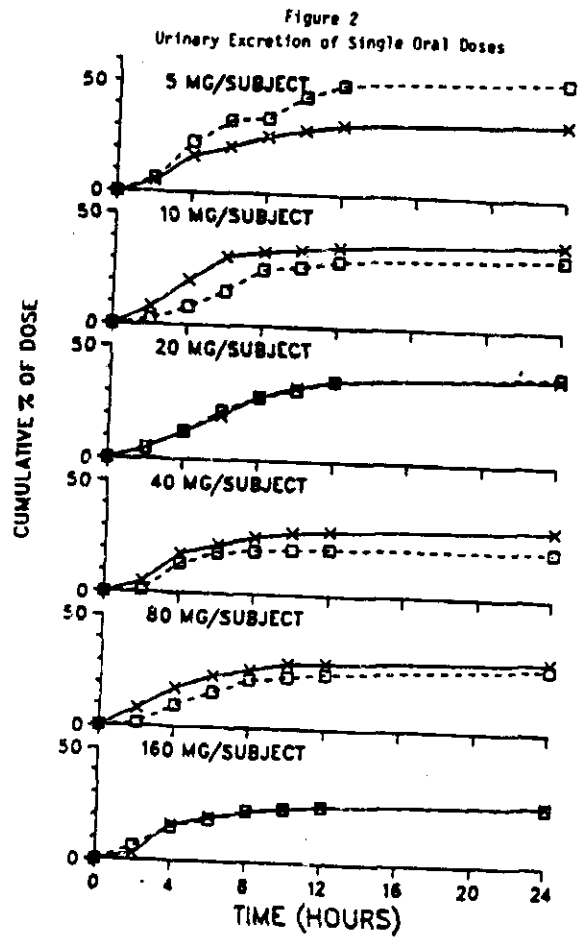


Figure 2
Urinary Excretion of Single Oral Doses



e. Conclusions: famotidine was well tolerated by healthy male volunteers when administered in single oral doses of 5 to 160 mg and in multiple 20 and 40 mg b.i.d. oral doses for 5 days. The drug was rapidly absorbed with peak levels at 2-3 hours proportional to the size of administered doses. Thirty to 40% of the drug was excreted in the urine; no accumulation was observed. No adverse effects were reported.

2. Study No. 1

a. Title: A double-blind, single, rising dose, placebo-controlled study to determine safety, tolerability and dose proportionality of blood and urine levels of famotidine administered orally to healthy volunteers.

b. Investigators: Miguel A. Zinny, M.D., Medical and Technical Research Associates, Needham, MA and Norman D. Grace, M.D., Tufts University School of Medicine, Boston.

c. Design of study: in this placebo-controlled study in 15 healthy volunteers, the subjects were admitted to the Clinical Research Unit the evening preceding each treatment period and remained confined to the unit until completion of the 48-hour treatment period. Following an overnight fast, the subjects received a single oral dose of famotidine 5, 10, 20 or 40 mg with a placebo control interspersed randomly in one of the treatment periods. Study periods were separated by intervals of one week. Vital signs were measured at 0, 2, 4, 8, 12, and 24 hours post-dosing. Laboratory safety parameters, including ECGs, were assessed before and after 24 hours of treatment at each study period. Plasma and urine samples collected at appropriate intervals were frozen for analysis at the sponsor's laboratories. At appropriate intervals post-treatment the subjects were asked about any unusual symptoms. In this and many of the following studies, symptoms were graded:

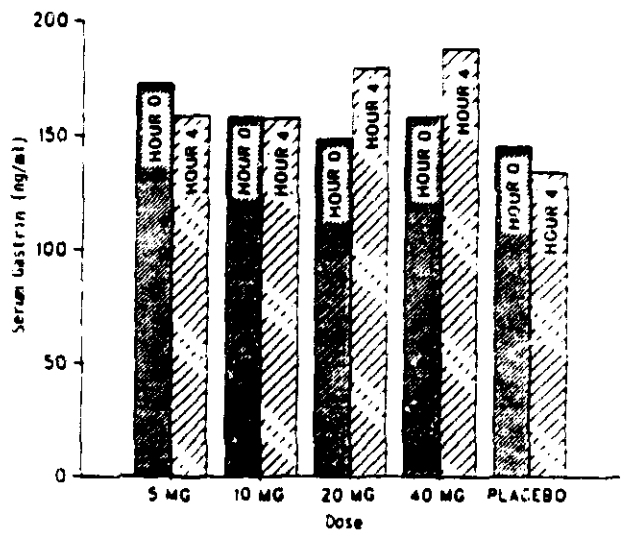
None:	no awareness of abnormal signs or symptoms
Mild:	aware of symptoms, but easily tolerated
Moderate:	discomfort enough to interfere with but not prevent daily activity
Severe:	unable to perform usual daily activities

d. Results

(1) Safety parameters: no abnormalities of vital signs, hemogram, serum electrolytes or urinalysis were observed with either famotidine or placebo. One of the subjects experienced transient lightheadedness after placebo. There were no other clinical adverse events.

(2) Serum gastrin (figure 3): mean serum gastrin levels at 0 hour were higher for all doses of famotidine than placebo. Four hours after treatment, mean gastrin levels were statistically significantly higher after the 20 and 40 mg doses than after the lower doses and placebo.

Figure 3
Mean Serum Gastrin 0-4 Hours Post-Dose N=15



(3) The results of serum prolactin determinations are described below under IID, "Hormonal effects."

e. Conclusions: famotidine is well-tolerated in single oral doses up to 40 mg. Doses of 20 mg and 40 mg increase serum gastrin.

3. Study No. 748

a. Title: A double-blind, placebo-controlled study to investigate the safety and tolerability of repeated doses of famotidine in healthy subjects.

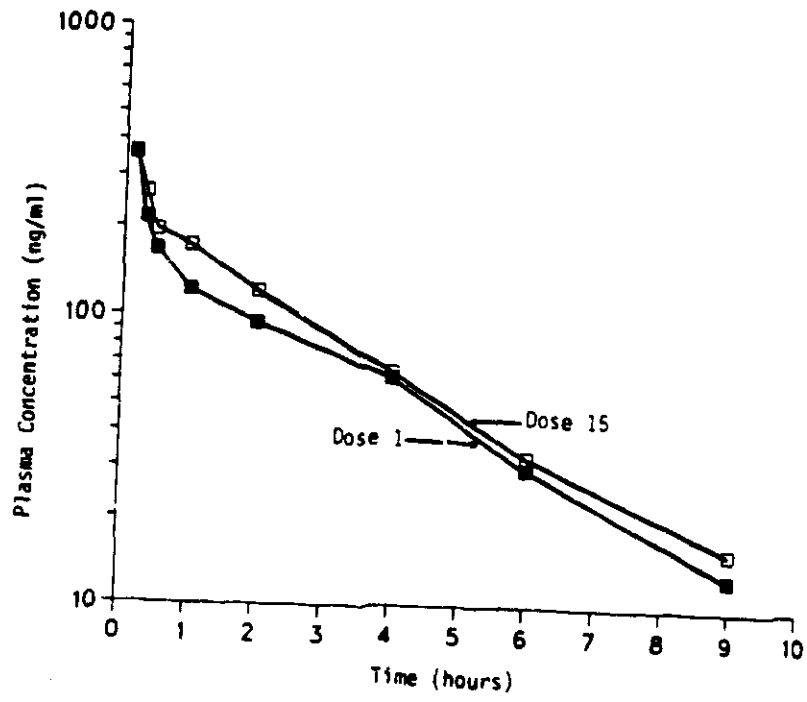
b. Investigator: Professor P. J. DeSchepper, Department of Pharmacology, Campus Gasthuisberg, Leuven, Belgium.

c. Design of study: at 0800 and 1700 hours for 7.5 days, the subjects received intravenous bolus injections of 5 ml containing either famotidine 20 mg (6 subjects) or placebo (2 subjects). Doses on odd-numbered days were administered in the left arm and on even numbered days in the right arm. Tolerability and safety were assessed by monitoring pain and induration at the injection site, ECG, vital signs, clinical chemistry, urinalysis, clinical adverse experiences and any changes in physical status. Plasma levels and urinary excretion of famotidine were determined after the first and 15th doses.

d. Results

(1) Plasma levels of famotidine (figure 4): the plasma is cleared rapidly of the administered drug with no evidence of a cumulative delay in clearance.

Figure 4
Mean Plasma Concentration of Famotidine
Following Single and Repeated I.V. Doses (N = 6)



(2) Safety: induration and local hyperemia occurred in 2 of the 6 famotidine treated subjects; in one of these, the investigator attributed the result to a slight extravasation of the drug during the last 15 seconds of the injection. Epigastric discomfort was reported by 3 famotidine and 1 placebo-treated subjects. A few laboratory safety parameters showed a statistically significant change after administration of both famotidine and placebo. No consistent changes were observed in physical examination or ECGs. A statistically significant decrease in systolic blood pressure was noted in subjects receiving placebo as well as in those receiving famotidine. Thus, clinical adverse experiences were few and they were similar for drug- and placebo-treated subjects.

e. Conclusions: famotidine 20 mg b.i.d. intravenously for 15 doses was well-tolerated in healthy subjects.

4. Summary of tolerance studies: In 3 studies in a total of 36 healthy volunteers famotidine was well tolerated in single oral doses up to 160 mg, in repetitive oral doses of 20 mg and 40 mg b.i.d. for 5 days, and in intravenous doses of 20 mg b.i.d. for 7.5 days. The only observation of possible clinical significance was a mild elevation of serum gastrin levels after oral administration of 20 and 40 mg. Additional tolerance data are derived from studies not designed primarily for this purpose.

B. Bioavailability/Pharmacokinetics

1. Study No. 748: the protocol has just been reviewed above under "Human Tolerance." The pharmacokinetic data derived from that study show (table 1) that after repeated administration of 20 mg twice daily for 15 doses, the drug was cleared primarily through the kidney and that the half-life was a little less than 3 hours.

TABLE 1

Pharmacokinetic parameters (geometric mean) of famotidine following repeat intravenous administration of 20 mg BID daily for 15 doses in 6 healthy subjects.

Plasma Clearance, ml/min	313
Renal Clearance, ml/min	259
Non-renal Clearance*, ml/min	54
Half-life, hours	2.7
Urinary Recovery, % of Dose	82.9

*Difference between plasma clearance and renal clearance.

2. Study No. 42

a. Title: An open, 4-way cross-over, single dose, comparative bioavailability study of famotidine capsules 20 mg, tablets 20 mg and 40 mg, and intravenous injection of 20 mg.

b. Investigator: Roger L. Williams, M.D., University of California, San Francisco, CA.

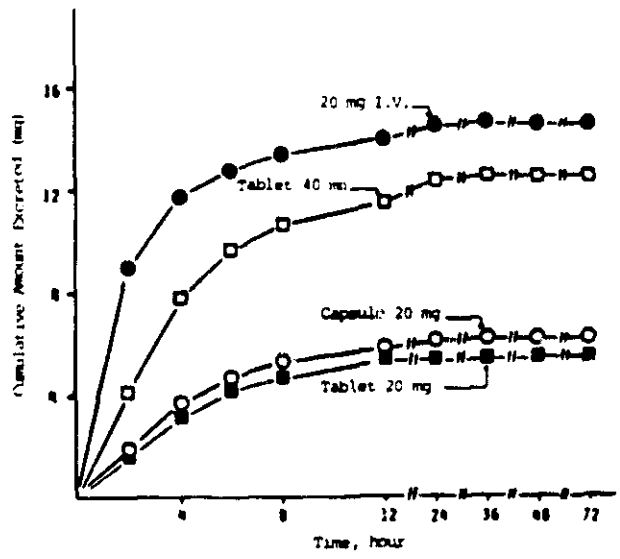
c. Design of study: this was an open, single-dose, 4-way cross-over study in 16 healthy volunteers assigned randomly to receive each of the 4 treatments listed in the title with a 1-week washout between treatments. Following administration of the test medications, plasma and urine samples were taken at appropriate intervals and were assayed for levels of famotidine.

d. Results

(1) Safety: no clinical or biochemical adverse experiences were reported at any time during the study.

(2) Pharmacokinetics: the time to maximum blood levels was the same for all 3 oral doses but reached a significantly higher level and remained higher for a longer period time with the 40 mg tablet. Approximately 30% of the drug was excreted in the urine over a 72 hour period after all 3 oral doses (figure 5), which was about half of the amount excreted after the intravenous dose. The total body clearance averaged approximately 28 l/h and the mean half-life was around 3 hours. For all practical purposes the 3 oral formulations had a similar bioavailability, approximating 45%.

Figure 5
Cumulative Amount of Famotidine Excreted in the Urine



e. Conclusions: single oral doses of famotidine, capsules 20 mg, tablets 20 mg or 40 mg, and IV dose of 20 mg, were well-tolerated. Systemic bioavailability approximated 45% and was similar for all 3 oral doses. The 20 mg capsule and 20 mg tablet are bioequivalent.

3. Study No. 556

a. Title: A two-part, open study in healthy elderly subjects to examine the pharmacokinetic profiles of famotidine when administered as a single intravenous and single oral dose (Part I) and repeated oral doses (Part II).

b. Investigator: B. Martin, M.D., Bios Consulting and Contract Research, Ltd., Surrey, England.

c. Design of study: open, two-part study in 8 healthy elderly subjects with random cross-over treatment sequence. During the first part of the study, fasting subjects received either a single intravenous dose of 20 mg or an oral dose of 40 mg. In the second part of the study they received 40 mg b.i.d. for 9 doses. Plasma and urine samples were collected according to the same schedule as that in the study reviewed above. Safety parameters were assessed by both clinical observation and conventional laboratory tests.

d. Results

(1) Safety: no drug-related adverse events were reported.

(2) Pharmacokinetics: plasma concentration of famotidine following the administration of a single oral dose or following the last of the multiple oral doses of 40 mg were similar (figure 6) as were the curves for urinary secretion of famotidine (figure 7). The disposition of the drug was therefore similar to that found in the younger volunteers reported in the study reviewed above. The bioavailability in these elderly subjects was 40%, i.e., in the same range as that in the younger subjects.

Figure 6
Plasma Concentration of Famotidine in Healthy Elderly (N=8)

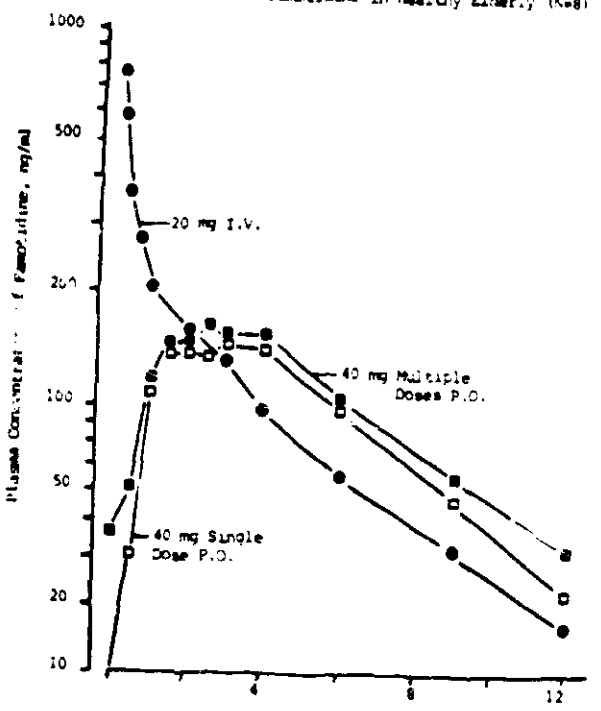
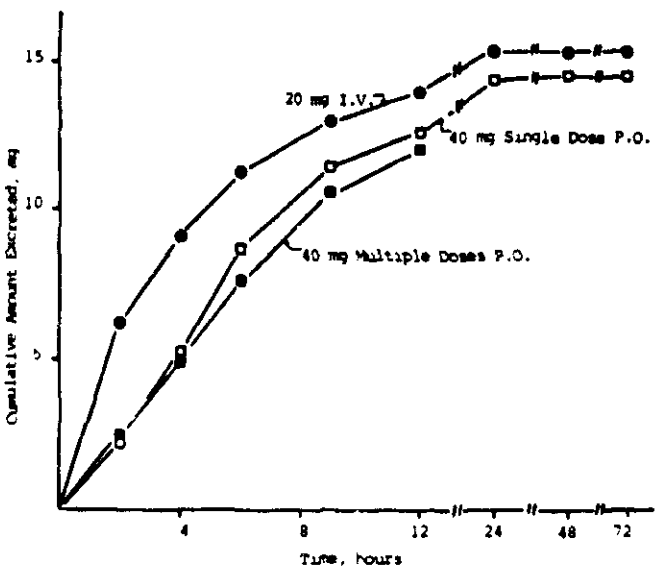


Figure 7
Cumulative Urinary Excretion of Famotidine in Healthy Elderly (N = 8)



e. Conclusions: The results of this study indicate that famotidine is as safe and as bioavailable in healthy elderly subjects as in the younger age group.

4. Study No. 527

a. Title: An open study to assess the disposition kinetics and safety of famotidine in patients with moderate to severe renal insufficiency.

b. Investigators: Paul Abraham, M.D. and William F. Keane, M.D., Drug Evaluation Unit, Regional Kidney Disease Program, Hennepin County Medical Center, Minneapolis, MN.

c. Design of study: 18 patients with moderate to severe renal insufficiency were assigned to one of three groups according to the degree of renal impairment. Group 1 (7 subjects) had a creatinine clearance of 30-50 ml/min and a serum creatinine greater than 3 mg %; the creatinine clearance in Group 2 (5 subjects) was 10-30 ml/min, in Group 3 (6 subjects) less than 10 ml/min. Patients in Group 3 were anuric; hemodialysis was disconnected one day prior to the administration of famotidine. On the study day a

single intravenous injection of famotidine 10 mg was given over a 1 minute period. Plasma and urine samples were collected according to essentially the same schedule as in the protocols reviewed above. Insulin and creatinine clearances were determined for 30 minute periods 1.5 hours before and 4 hours after administration of the drug. The patients were observed for any adverse clinical reactions; conventional laboratory tests were performed before and after drug administration.

d. Results

(1) Safety: no clinically important drug-related adverse events occurred during this study.

(2) Pharmacokinetics: in patients with impairment of renal function plasma clearance (figure 8) and renal clearance (figure 9) of the drug are diminished pari passu with the degree of renal impairment. The total area under the curve (figure 10) and the half-life (figure 11) are inversely proportional to the creatinine clearance. The non-renal clearance was not affected by the degree of impairment of renal function. Considering that the upper limit of half-life in healthy young and healthy elderly subjects was in the neighborhood of 5 hours, it is apparent that the half-life of famotidine becomes prolonged with a degree of renal impairment characterized by a creatinine clearance of less than 30 ml/min.

Figure 8
Renal Function and Plasma Clearance in Renal Impaired Patients

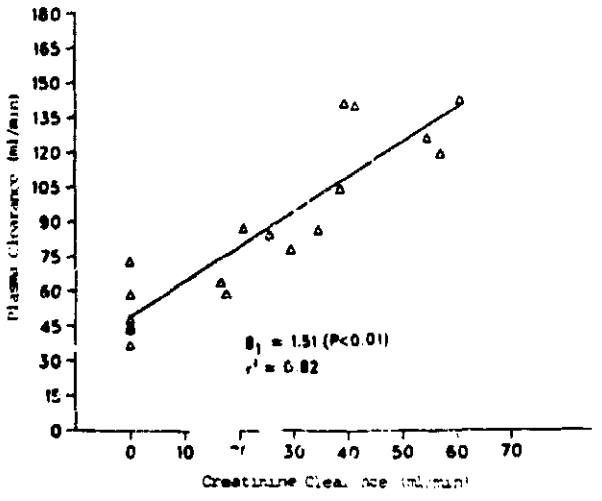


Figure 9
Renal Function and Renal Clearance in Renal Impaired Patients

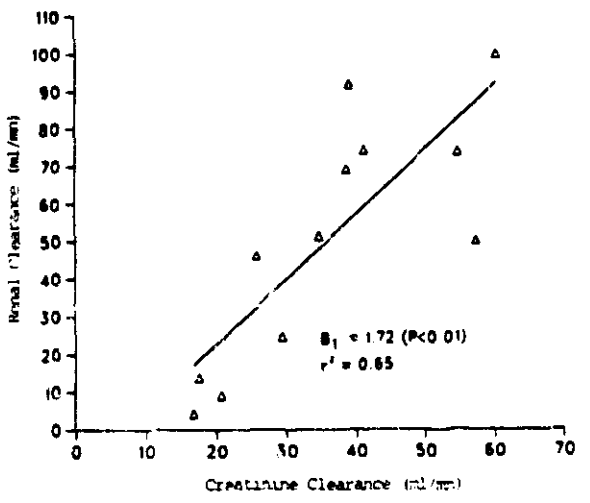


Figure 10
Renal Function and Total Area Under the Curve in Renal Impaired Patients

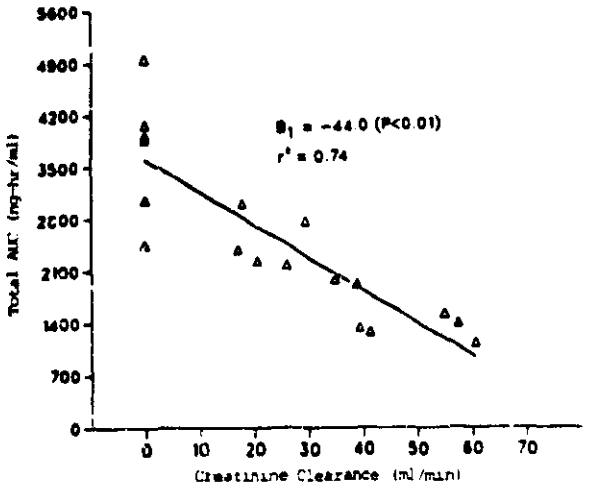
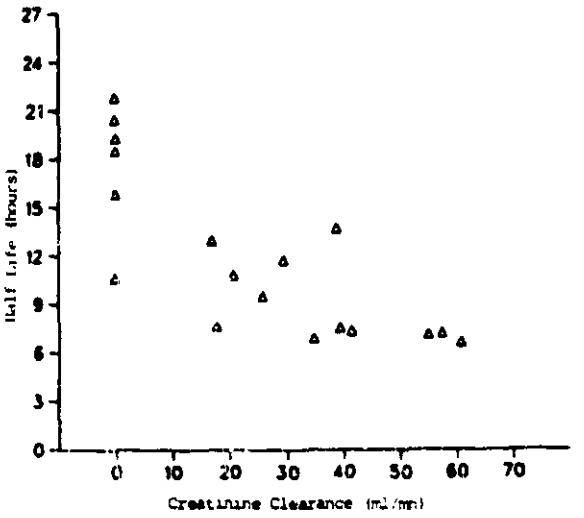


Figure 11
Renal Function and Plasma Half Life in Renal Impaired Patients

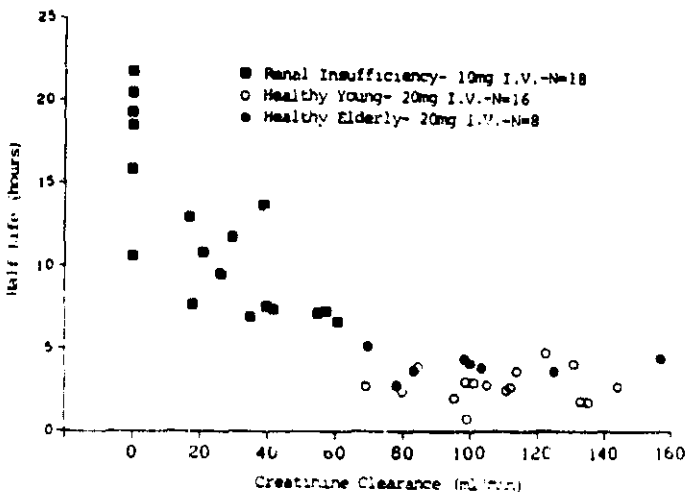


Note: Since the relationship between plasma elimination half-life and renal function is known to be non-linear, simple linear regression analysis was not performed.

e. Conclusion: the results of all parameters of disposition of famotidine in patients with decreased renal function indicate that in patients with creatinine clearance of less than 30 ml/min the dosage of famotidine must be adjusted downward to achieve blood levels comparable with those obtainable at any given dose in patients with normal renal function or with lesser degrees of renal impairment.

5. Summary of bioavailability/pharmacokinetic studies: the results of 4 studies evaluating famotidine in single intravenous doses of 10 mg and 20 mg, single oral doses of 10 mg, 20 mg and 40 mg, and multiple oral doses of 40 mg indicate that the drug is 40-45% bioavailable, has a mean half-life of about 3 hours and is cleared from the body primarily via the kidneys. The pharmacokinetics are approximately the same in elderly as in younger subjects, while in patients with renal insufficiency significant delay in excretion of the drug appears when the degree of renal impairment amounts to a creatinine clearance of less than 30 ml/min. A reduction in the famotidine dose would therefore be indicated in such patients. The comparative half-lives of famotidine in the healthy young, the healthy elderly and the renally-impaired subjects are shown graphically in figure 12. No drug-related adverse effects were documented in any of these studies.

Figure 12
Relationship of Famotidine Half Life to Creatinine Clearance



C. Gastric and pancreatic function

1. Pentagastrin-stimulated gastric secretion

a. Study No. 725

(1) Title of study: Comparison of 3 different doses of famotidine on pentagastrin-stimulated gastric acid secretion.

(2) Investigator: Professor Richard H. Hunt, McMaster University Medical Centre, Hamilton, Canada.

(3) Design of study: double-blind, four-way, placebo-controlled, cross-over study in which 8 healthy volunteers were assigned randomly to receive 3 dosage regimens of famotidine intravenously to achieve plasma concentrations of 10, 30 and 90 ng/ml respectively, or placebo. In the morning after an overnight fast the subjects were intubated with a 14 French double-lumen tube, the contents of the stomach emptied, and continuous aspiration carried out for 7 consecutive hours. The first hour assessed basal acid secretion. A 19-gauge butterfly needle was then inserted into a vein in each forearm to provide for administration of pentagastrin and test drugs separately. A loading dose of famotidine was administered as a bolus injection over 2 minutes and constant infusion started immediately thereafter at a rate to provide the desired blood level. The amounts of famotidine administered were:

Plasma concentrations ng/ml	Loading dose (2 min) mcg/kg	Rate of infusion mcg/kg/hr
10	3	4.3
30	9	12.9
90	27	38.7

The placebo arm consisted of saline infused at a rate of 50 ml/h. At the end of the first 2 hours pentagastrin infusions were administered in 5 incremental infusion rates, each for a period of 1 hour, starting with 0.1 mcg/kg/h and ending with 2.0 mcg/kg/h. Blood samples for assay for famotidine were obtained at baseline and at hourly intervals for 7 hours. The volume of gastric secretion was measured every 10 minutes and analyzed for pH, titratable acidity and pepsin concentration. The first 30 minutes of each hour was considered a stabilizing stage; the collections of the last three 10-minute intervals of each hour were averaged and doubled to obtain the hourly rates of secretion. Observations to assess safety included a hemogram, clinical chemistry and urinalysis.

(4) Results

(a) Safety: no drug-related adverse events occurred during these studies.

(b) Gastric secretion: 8 volunteers completed the studies. During pentagastrin stimulation, famotidine significantly reduced gastric acid output in a dose-related fashion, reaching almost 100% inhibition with the highest plasma concentration of the drug (figure 13), an effect resulting from reduction in both the volume (figure 14) and the concentration (figure 15) of acid. Paradoxically, a sustained elevation of pH was observed with only the dose which yielded a blood level of 90 ng/ml (figure 16). Pepsin concentration was not significantly different with the 3 doses than with placebo, but as a result of the great reduction in volume the pepsin output was correspondingly reduced.

Figure 13
Mean Acid Output For Each Ten-Minute Collection (N=8)

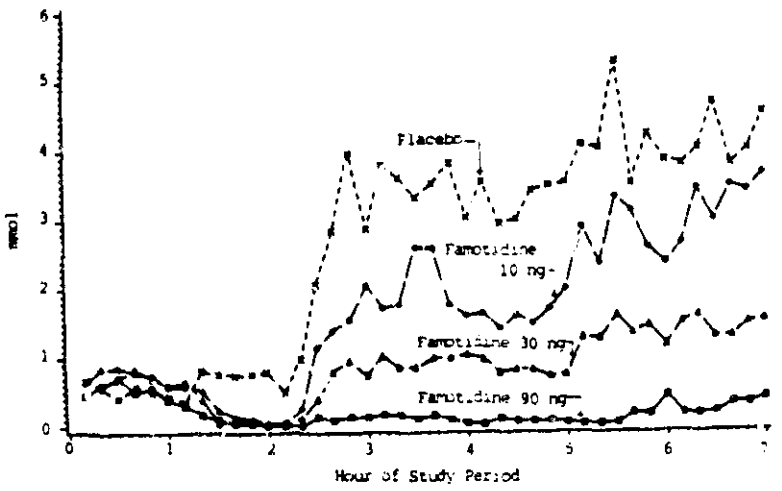


Figure 14
Mean Volume For Each Ten-Minute Collection (N=8)

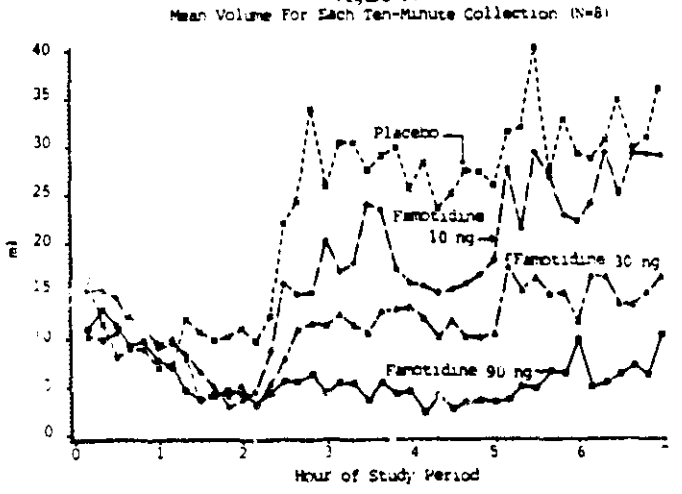


Figure 15
Mean Acid Concentration For Each Ten-Minute Collection (N=8)

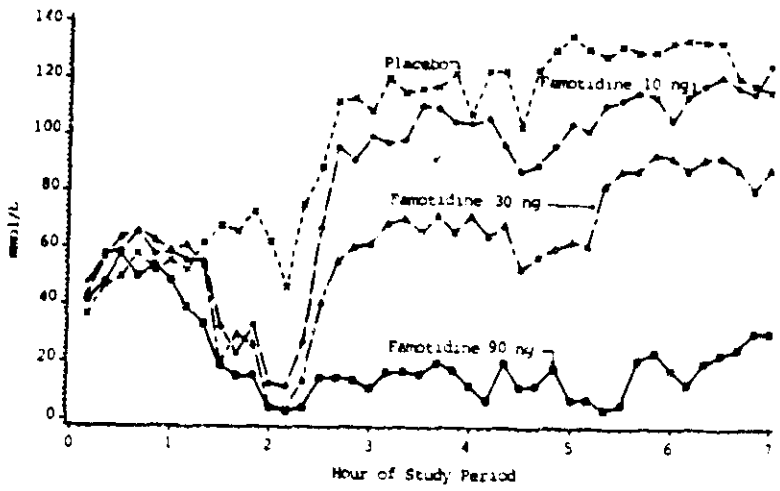
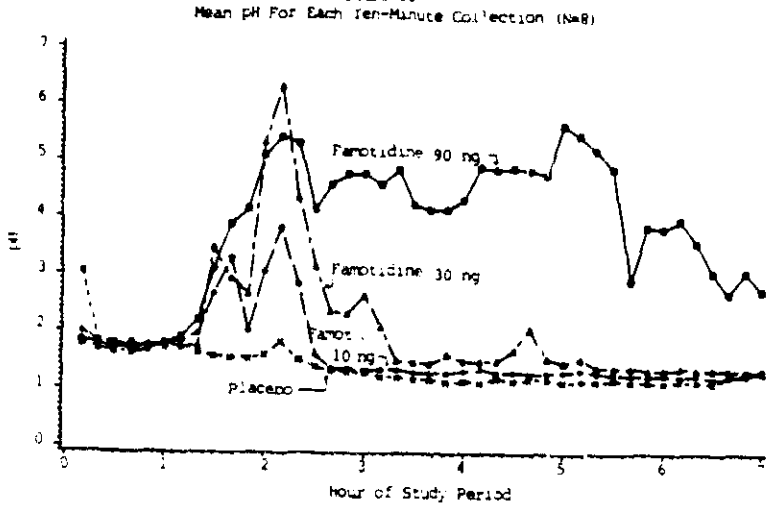


Figure 16
Mean pH For Each Ten-Minute Collection (N=8)



(5) Conclusions: constant intravenous infusions of famotidine at rates estimated to produce plasma concentrations of 10, 30, and 90 ng/ml inhibited basal gastric secretion maximally and pentagastrin-stimulated secretion in a concentration-dependent manner. At a concentration of 90 ng/ml acid secretion is almost completely inhibited. The sponsor concludes that for maximal therapeutic antisecretory effects, this level of plasma concentration might be desirable.

(6) Comment: the investigator must have had some basis for knowing a priori what rates of infusion would produce the desired blood levels. It will be interesting to hear from the sponsor how it was done.

b. Study No. 2

(1) Title: A double-blind, placebo and active controlled study to determine the effect of three separate incremental oral doses of famotidine on pentagastrin-stimulated gastric acid secretion in healthy volunteers.

(2) Investigator: J. Lacey Smith, M.D., Baylor College of Medicine, Houston, TX.

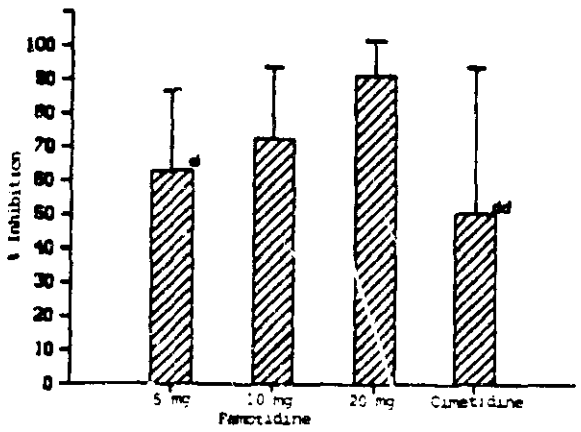
(3) Design of Study: double-blind, cross-over, placebo and active drug (cimetidine) controlled study. Ten healthy volunteers eligible for the study on the basis of medical history, physical examination, laboratory tests and ECGs received single doses of famotidine 5, 10, and 20 mg placebo, or cimetidine 300 mg all administered orally with water 200 ml. The subjects remained ambulatory for 1 1/4 hours and were then intubated with a 16 French double-lumen tube. Volume of secretions lost through the pylorus was corrected by infusion of a standard solution of phenol-red. Gastric aspirates were collected for three 15-minute intervals followed by IM injection of pentagastrin 6 ug/kg, followed by 15-minute collections of the continuously aspirated secretions for one hour. An additional investigation enlisted 6 of the volunteers who were found to be high basal acid secretors (more than 2.0 mEq/h) and/or brisk responders to pentagastrin (more than 20 mEq/h) in a study to assess the effect of famotidine 20 mg administered orally at 8 p.m. on the gastric secretory response to a single IM dose of pentagastrin given 10 and 12 hours later.

(4) Results

(a) Safety: no adverse events occurred during this study.

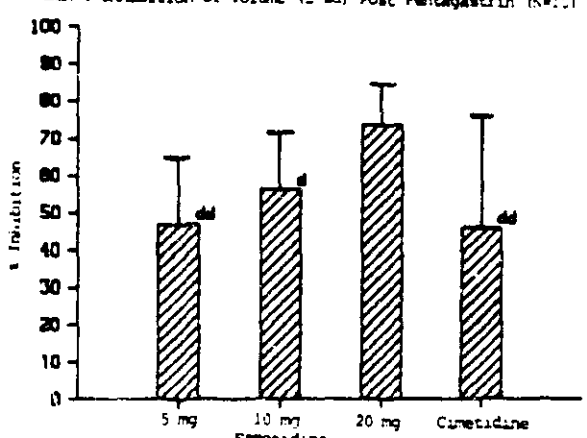
(b) Gastric secretion: pentagastrin-stimulated acid output was inhibited by famotidine in a dose-related fashion (figure 17), a result primarily of inhibition of volume of secretion (figure 18). The percent inhibition with cimetidine 300 mg was of the same order as that with famotidine 5 mg. Basal gastric secretion was decreased by all active treatments in comparison with placebo. Among the 6 subjects in the additional study, inhibition of pentagastrin-stimulated acid secretion 10-12 hours following famotidine 20 mg ranged from 18% to 88% with a mean of 53.6%.

Figure 17
Mean % Inhibition of Acid (± sd) Post Pentagastrin (N=10)



d, dd significantly different than famotidine 20 mg, $p<0.05$, $p<0.01$ respectively

Figure 18
Mean % Inhibition of Volume (± sd) Post Pentagastrin (N=10)



d,dd significantly different than famotidine 20 mg, $p<0.05$, $p<0.01$ respectively

(5) Conclusion: Famotidine administered orally approximately one hour before intramuscular injection of pentagastrin inhibited the gastric secretion in the following hour significantly more than did placebo with all doses tested. The inhibitory effect of famotidine 5 mg was comparable to that of cimetidine 300 mg. Famotidine 20 mg diminished the secretory response in varying degrees to an injection of pentagastrin given up to 11 hours later.

c. Study No. 3

(1) Title of Study: A double-blind placebo and active drug-controlled study to determine the effect of three separate incremental oral doses of famotidine on pentagastrin-stimulated gastric acid secretion in healthy volunteers.

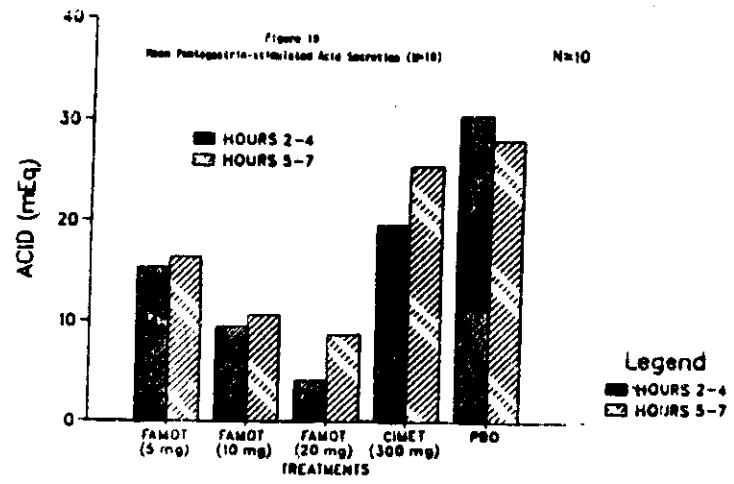
(2) Investigator: Richard W. McCallum, M.D., Yale University School of Medicine, New Haven, CT.

(3) Design of Study: double-blind, cross-over, placebo and active drug study in a 10 healthy volunteers. The procedure was similar to that of study No. 2 except that pentagastrin was infused intravenously at a rate of 1 mcg/kg/hr for two hours starting two hours after oral administration of famotidine 5, 10 or 20 mg, or cimetidine 300 mg or placebo. At the conclusion of the infusion, the subjects were permitted to become ambulatory for one hour after which a second continuous two-hour pentagastrin infusion was started. At the completion of this infusion, which was seven hours after administration of the test substance, the study day was completed.

(4) Results

(a) Safety: no drug-related adverse events were reported.

(b) Gastric secretion: a dose-related reduction in acid output following famotidine was observed after both pentagastrin-stimulated periods (figure 19). During the first period of stimulation acid output with famotidine 5, 10 and 20 mg was reduced 50%, 69% and 87% respectively, compared to 36% for cimetidine. During the second period of stimulation the respective degrees of inhibition were 41%, 62%, 69% and 7%.



(5) Conclusion: the results confirm those of the previous study in showing that famotidine inhibits pentagastrin-stimulated gastric acid output in a dose-related fashion for at least 7 hours after oral administration of the drug. In this study, moreover, the degree of inhibition with famotidine 5 mg was both greater and more prolonged than with cimetidine 300 mg.

d. Study No. 5

(1) Title: A double-blind, placebo controlled study to determine the effect of three separate incremental oral doses of famotidine on nocturnal and pentagastrin-stimulated gastric acid secretion in healthy volunteers.

(2) Investigator: Sidney Cohen, M.D., and Ann Ouyang, M.D., Hospital of the University of Pennsylvania, Philadelphia, PA.

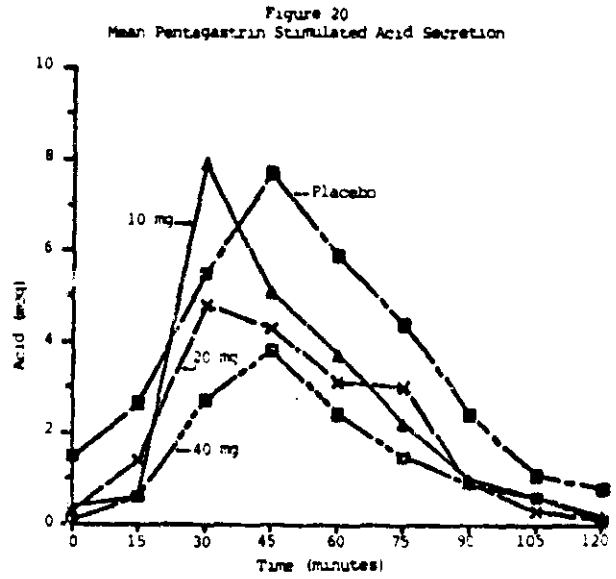
(3) Design of Study: the effects of single oral doses of famotidine 10, 20 and 40 mg were compared to placebo on pentagastrin-stimulated gastric acid secretion 9 1/2 hours after administration of the drug in 8 healthy volunteers in a double-blind, four-period cross-over study with a washout interval of 72 hours separating the treatments. The medication or placebo was self-administered at midnight. Pentagastrin 6 ug/kg was given subcutaneously 9 1/2 hours after ingestion of the drug; gastric secretion was determined for two hours thereafter.

(4) Results

(a) Safety: the only adverse experiences were those attributable to administration of pentagastrin.

(b) Gastric secretion (figure 20): during the first hour of pentagastrin stimulation there were statistically significant reductions of gastric acid output with famotidine 20 mg and 40 mg compared to placebo; during the second hour significant reduction of acid output occurred with all 3 doses of famotidine.

Figure 20
Mean Pentagastrin Stimulated Acid Secretion



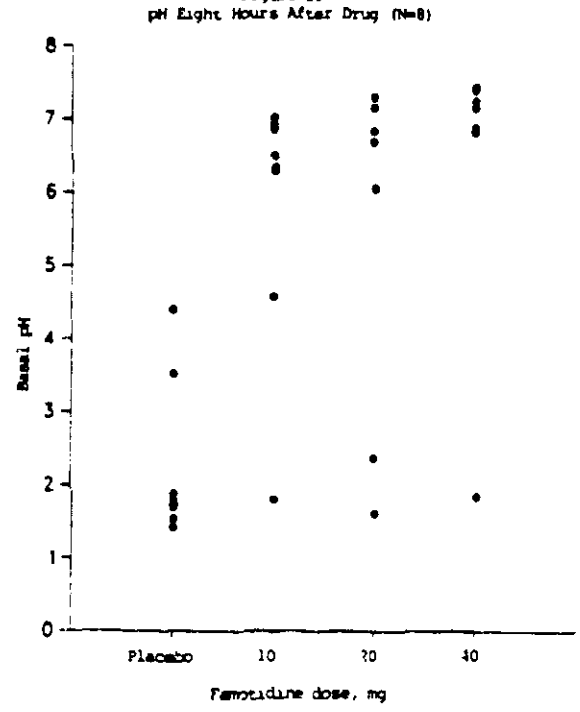
(5) Conclusion: Famotidine in single oral doses of 10, 20 and 40 mg inhibits pentagastrin stimulated volume and acidity of gastric secretion in a dose-related manner for a period of more than 11 hours.

e. Summary of studies on pentagastrin-stimulated secretion: famotidine in the proposed daily therapeutic doses (40 mg h.s. for short-term treatment of peptic ulcer, 20 mg h.s. for prevention of recurrence) inhibits acid secretion stimulated by pentagastrin administered by continuous IV, intramuscular or subcutaneous injection. The inhibition amounts to 60-70% compared to placebo, and lasts for up to 12 hours in some cases. A single oral dose of 5 mg has approximately the same inhibitory effect as a dose of 300 mg of cimetidine.

2. Nocturnal secretion

a. Study No. 5: the protocol was as reviewed above under IIC1d. The pH of nocturnal gastric secretion was elevated (figure 21) by single oral doses of famotidine 10, 20 and 40 mg for at least 8 hours. The pH values were above 6 in only 1 of the 8 subjects on placebo contrasted with 5 on famotidine. With the 40 mg dose the pH in all 8 subjects was above 7.0.

Figure 21
pH Eight Hours After Drug (N=8)



b. Study No. 7

(1) Title: A double-blind, placebo-controlled study to determine the effects of four oral dose levels of famotidine at the beginning and end of a 5-day dosing regimen on nocturnal and food stimulated acid secretion in volunteers who are hyper-secretors.

(2) Investigator: Jerome Ryan, M.D., Clinical Research Center, Inc., New Orleans, LA.

(3) Design of Study: the study was divided into three parts:

Part I evaluated nocturnal and food-stimulated acid secretion on the first and fifth day when doses of famotidine 5, 10, 20 and 40 mg and placebo were administered to 4 healthy volunteers at 9:00 PM each evening for 5 days. Each treatment period was separated by a 5 day interval. The study was discontinued when it became apparent that an effective dose had not been identified with the dosage regimens evaluated. Other dosage regimens were then explored in an open-label pilot study.

Part II evaluated the effects on nocturnal and meal-stimulated acid secretion over a 22-hour interval after administration of famotidine 40 or 80 mg or placebo at 7:00 AM in an open-label design to 2 healthy volunteers. Each treatment period was separated by an interval of 5 days.

Part III evaluated the effects on nocturnal and meal stimulated acid secretions over a 22-hour interval with dosage regimens of famotidine 10 mg b.i.d., 20 mg b.i.d., 80 mg at 9:00 PM or placebo in an open-label design to 3 healthy volunteers. Each treatment period was separated by an interval of 5 days. Volunteers were acceptable for the study on the basis of a basal secretory rate greater than 5 mEq/h.

(4) Results: nocturnal acid output measured from 12 midnight to 7:00 AM after a dose of drug at 9:00 PM was inhibited by about 90% by both a 40 and 80 mg dose of famotidine.

(5) Conclusion: effective inhibition of nocturnal acid secretion can be achieved with a single oral dose of famotidine 40 mg h.s. The effect on food-stimulated secretion will be discussed under that heading.

c. Study No. 51

(1) Title: A double-blind, placebo-controlled, randomized 3-way cross-over study in ambulatory duodenal ulcer patients in remission to evaluate the effect of famotidine on 24 hour intragastric pH profile and concurrent gastrin values.

(2) Investigator: J. Lacey Smith, M.D., Baylor College of Medicine, Houston, TX.

(3) Design of Study: duodenal ulcer patients in remission with a basal acid secretion greater than 5 mEq/h were assigned randomly to receive either placebo at 9:00 AM and 9:00 PM, famotidine 20 mg at 9:00 AM and 9:00 PM or placebo at 9:00 AM and famotidine 40 mg at 9:00 PM. Study day 7 of each treatment period was designated as monitoring day during which the 24 hour intragastric profile was monitored continuously and blood samples collected for measurement of serum gastrin. On all monitoring days the patients were given a choice of foods from a menu providing for the same intake of xanthine-containing foods and beverages. Meal times were 8:30 AM, 12 M and 5:00 pm. Four subjects completed the study.

(4) Results

(a) Safety: no drug-related adverse events were reported.

(b) Nocturnal acidity (table 2): the median and ranges of pH measured from 1:00 AM to 9:00 AM were placebo 1.38 (1.20-2.38), famotidine 40 mg at 9:00 PM 5.88 (3.90-6.05) and famotidine 20 mg at 9:00 AM and 9:00 PM 5.53 (3.92-6.97).

TABLE 2

Effect of famotidine on nocturnal acidity
Famotidine or placebo given orally at 9:00 PM
Mean intragastric pH measurements, 1:00 AM - 9:00 AM

Patient	Famotidine 40 mg	Famotidine 20 mg	Placebo
1	6.05	6.97	1.38
2	3.90	4.94	1.20
3	5.80	3.92	2.38
5	5.95	6.11	1.38
Median	5.88	5.53	1.38
Range	3.90-6.05	3.92-6.97	1.20-2.38

(c) Food stimulated secretion is discussed below under IIC3a.

(5) Conclusion: in duodenal ulcer patients in remission, the pH of nocturnal gastric secretion was significantly higher in patients receiving famotidine than in those receiving placebo.

d. Summary of studies on nocturnal secretion: the proposed therapeutic doses of famotidine (40 h.s. for short-term treatment, 20 h.s. for prevention of recurrence) reduce nocturnal acid production by 85-95% and increase intragastric pH to as high as 4 to 7 compared to placebo levels up to 2.4.

3. Food-stimulated secretion

a. Study No. 7: this is the study described above (IIC2b) in which the effect on nocturnal secretion was reviewed.

(1) Results

(a) Safety: no serious adverse reactions attributable to famotidine were reported.

(b) Acidity: a significant increase in the pH following breakfast was observed as a carryover of the effect of the 20 mg b.i.d. and 40 mg h.s. doses compared to placebo (table 3). Neither the previous h.s. dose of 40 mg nor the dose of 20 mg at 9:00 AM had any effect on the pH following the evening meal.

TABLE 3

Effect of famotidine on acidity of food-stimulated gastric secretion

Patient	Mean intragastric pH 9:00 AM - 5:00 PM			5:00 PM - 1:00 AM		
	40 mg HS	20 mg BID	Placebo	40 mg HS	20 mg BID	Placebo
1	3.32	3.35	1.99	1.47	1.75	1.63
2	2.82	3.08	2.07	2.36	1.77	1.29
3	2.21	2.78	1.99	1.42	2.34	1.72
5	2.80	3.20	1.96	1.54	2.11	1.97
Median	2.81	3.14	1.99	1.51	1.94	1.68
Range	2.21-3.32	2.78-3.35	1.96-2.07	1.42-2.36	1.75-2.34	1.29-1.97

(c) Conclusion: a single h.s. dose of famotidine 20 or 40 mg has a moderate inhibitory effect on the gastric secretory response to breakfast on the following morning, but no effect on meals later in the day.

b. Study No. 51: the procedure and the effect on nocturnal secretion were reviewed above under IIC2c.

(1) Results

(a) Safety: the only clinical adverse experience occurred in a patient receiving placebo. The same subject also had an increase in band cells. One subject receiving famotidine 40 mg h.s. experienced transient pyuria, not considered drug-related.

(b) Effect on pH of digestive secretions: the mean pH measurements for each volunteer over the 9:00 AM to 5:00 PM interval were higher during administration of famotidine than during placebo, but the data were insufficient for statistical analysis.

c. Summary of studies on food stimulated secretion: insufficient data are available to permit conclusions regarding the effects of famotidine on food stimulated secretion in duodenal ulcer patients in remission. In healthy volunteers doses of 20 and 40 mg h.s. show a carry-over inhibitory effect on breakfast-stimulated acid output.

4. Gastric emptying and pancreatic secretion

a. Study No. 61

(1) Title of study: An open-label study to evaluate the effect of treatment with famotidine on gastric emptying and pancreatic exocrine secretion in healthy volunteers.

(2) Investigator: Richard Redinger, M.D., University of Louisville, Louisville, KY.

(3) Design of study: in 6 healthy male volunteers receiving famotidine 40 mg b.i.d for 7 days, labeled chicken pate in beef stew was used to measure the gastric emptying time of a solid meal, and pancreatic exocrine function was assessed by measuring volume, bicarbonate and amylase after intravenous secretin, before and after 7 days of treatment.

(4) Results

(a) Safety: No clinical adverse experiences or clinically important changes in laboratory parameters were observed.

(b) Gastric emptying: famotidine had no significant effect on gastric emptying.

(c) Pancreatic exocrine function: mean volume of secretion (figure 22) was not affected by famotidine; there was a trend towards a reduction in the output of bicarbonate (figure 23) and amylase (figure 24) but the differences were not significant.

Figure 22
Mean Cumulative Volume (ml) of Duodenal Juice

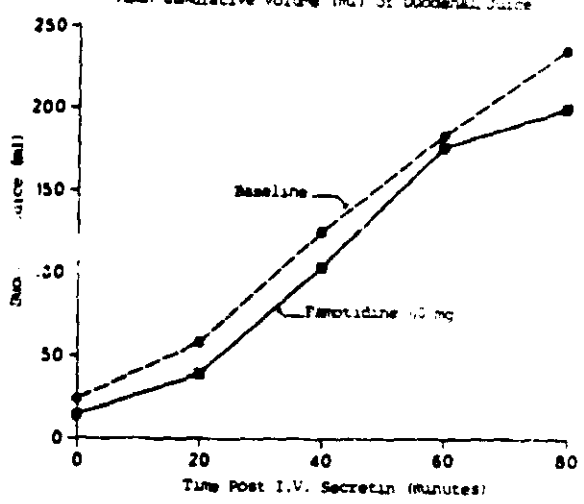


Figure 23
Bicarbonate, Mean Cumulative Total (mEq)

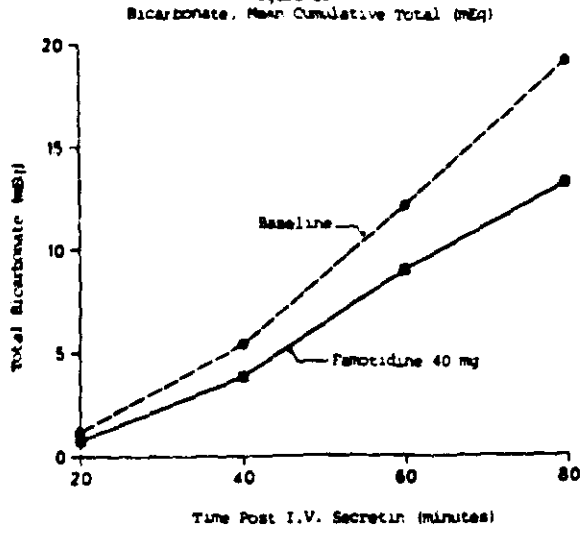
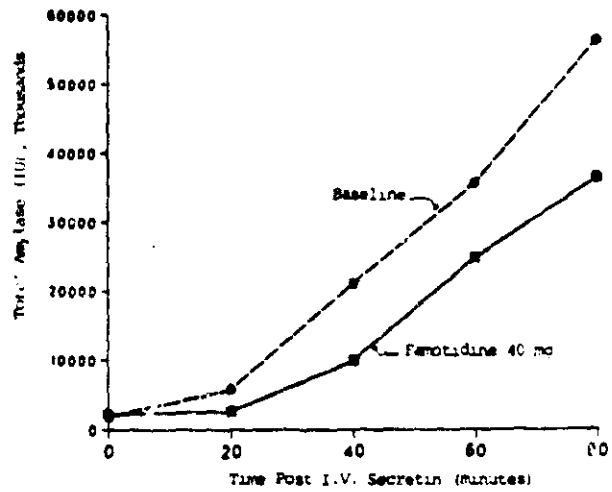


Figure 24
Amylase, Mean Cumulative Total (IU)



(d) Conclusion: on the basis of the limited amount of data available from this one study there appears to be no significant effect of famotidine on gastric emptying or pancreatic exocrine secretion.

(e) Comment: the trend toward reduction of volume and especially of bicarbonate output after administration of famotidine may indicate a real effect. The less acid reaching the upper intestine, the less release of secretin and the less stimulus to these functions of the pancreas. This possibility could be better evaluated by determining the effect of famotidine on the basal secretions of the pancreas.

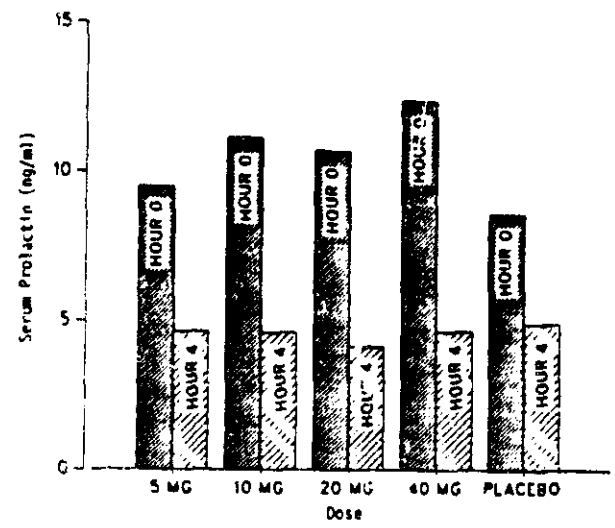
5. Summary of effects on gastric and pancreatic function: famotidine suppressed basal, food-stimulated nocturnal and pentagastrin stimulated volume and acidity of gastric secretion in a dose-related manner. The dose recommended for short-term treatment of peptic ulcer (40 mg h.s.) inhibited nocturnal secretion almost completely and had a significant carry-over effect on the acid response to a breakfast meal or an injection of pentagastrin secretion on the following morning. Pepsin concentration was not affected, but pepsin output was reduced in consequence of the reduction in volume of secretion. Famotidine had no effect on the rate of gastric emptying of a meal, nor, apparently, on secretin-stimulated pancreatic secretion.

D. Hormonal effects

1. Study No. 1: the protocol was described under "Human tolerance", (IIA2).

Effect on serum prolactin (figure 25): mean prolactin levels with all drug doses were higher at 0 hour than with placebo; these differences were thought to be attributable to the inherent variations of measurement. Four hours after dosing, significant mean decreases from 0 hour were observed for all treatments, probably reflecting diurnal variation.

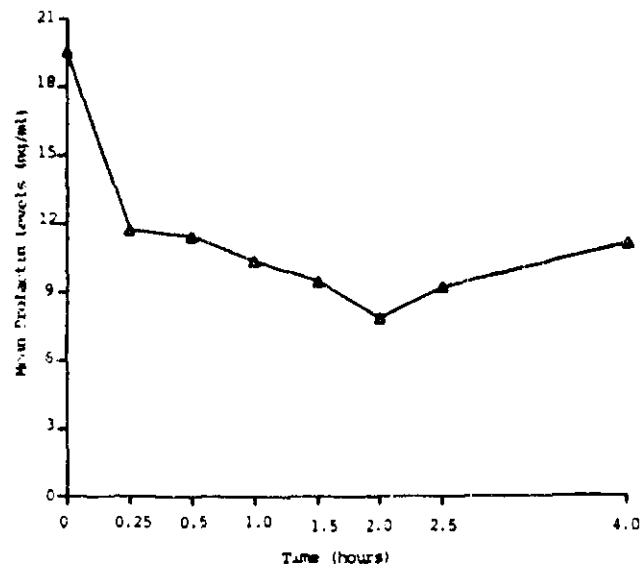
Figure25
Mean Serum Prolactin 0-4 Hours Post-Dose (N=15)



2. Study No. 42: the protocol was reviewed under "Human Tolerance" (IIA2).

Effect on secretion of prolactin (figure 26): prolactin levels assessed over a period of 4 hours following intravenous administration of famotidine 20 mg were significantly lower than the pre-drug levels. The sponsor speculates that this might be because the baseline blood samples were obtained immediately after the subjects had stopped being ambulatory, whereas the post-drug samples were obtained while the subjects had been recumbent for some time. Also, the known diurnal variation in serum prolactin levels may have been a factor. At any rate, famotidine 20 mg administered intravenously did not stimulate prolactin secretion.

Figure 26
Mean Prolactin Levels Following Intravenous Administration



3. Study No. 31

a. Title of study: A double-blind, dose-ranging study to evaluate the effects on healing of active duodenal ulcer, famotidine compared to placebo.

b. Investigator: Ram K. Shrivastava, M.D., New York, New York.

c. Design of study: an addendum was made to this study to include measurement of selected hormones. Blood samples were taken at baseline and at the end of the short-term treatment of duodenal ulcer for determination of prolactin, FSH and LH, gastrin, and, in males, testosterone.

d. Results: some or all of the parameters were tested in up to 10 patients. Minor changes, not clinically important, were recorded, suggesting that famotidine has no effect on the hormones measured.

e. Conclusion: in this limited number of subjects, there was no apparent drug-related effect on hormone levels.

4. Summary of hormonal affects: famotidine did not stimulate the release of prolactin, FSH, LH or testosterone. Since there were no comparative studies with other H_2-blockers, the significance of these findings is questionable. An inhibitory effect of famotidine on prolactin secretion is not ruled out by the data submitted.

E. Drug interactions

1. Study No. 48

a. Title of study: An open label, randomized, 2-way, cross-over study to assess the effect of famotidine and of cimetidine on the disposition of intravenous theophylline.

b. Investigator: Roger L. Williams, M.D., University of California, San Francisco, CA.

c. Design of study: an open, randomized, 2-way cross-over study in healthy volunteers to determine the effect of multiple oral doses of famotidine and cimetidine on the pharmacokinetics of intravenous theophylline as measured by plasma concentrations and urinary recovery.

The pharmacokinetics of famotidine after single and multiple doses were also examined. The study was carried out in 10 healthy volunteers, 5 of each sex, ages 21-32, mean 24.5 years. Each study period was of 9 days duration and divided into 3 parts. Part 1 was a baseline segment consisting of the initial 2 days in which aminophylline (85% theophylline) 5 mg/kg was administered IV and plasma and urine collected to establish

baseline concentrations of theophylline. Part 2 was a 1-day no-treatment washout segment. Part 3 was a drug treatment segment in which either famotidine 40 mg b.i.d. or cimetidine 300 mg q.i.d. was administered for 3 days and plasma and urine collected to establish single-dose and repeat-dose plasma concentrations of famotidine but not cimetidine. On the fourth day, aminophylline was given concomitantly with famotidine or cimetidine. Plasma and urine were collected for both drug groups for 48 hours and the findings compared with the baseline theophylline period. A minimum 7 day washout period separated the study periods. Adverse reactions were monitored throughout.

d. Results:

(1) Safety: no adverse clinical or laboratory events attributable to famotidine or cimetidine were reported.

(2) Disposition of theophylline: total body clearance of theophylline was unchanged by famotidine (58 vs 61 ml/min), but was significantly decreased by cimetidine (58 vs 40 ml/min), p 0.01. The half-life of theophylline remained constant during treatment with famotidine, but was significantly prolonged (9.3 to 12.2 h), p 0.05, with cimetidine. Plasma concentration (figure 27) and urinary excretion (figure 28) of theophylline remained unchanged during treatment with famotidine, but plasma concentration was increased and urinary recovery prolonged during treatment with cimetidine.

Figure 27
Plasma Concentration of Theophylline
After I.V. Administration of 5 mg/kg Theophylline

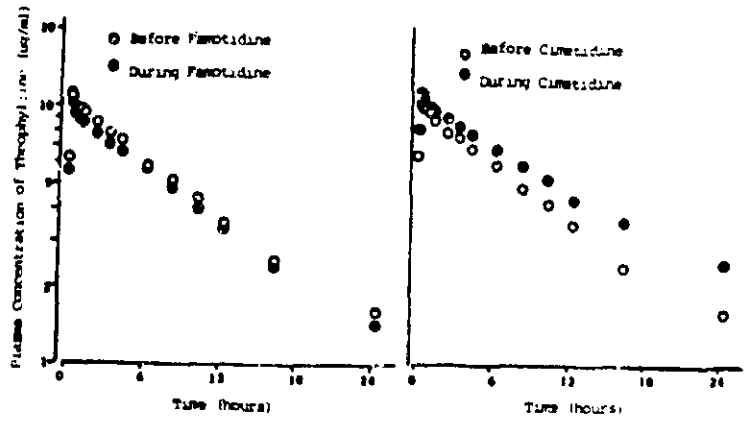
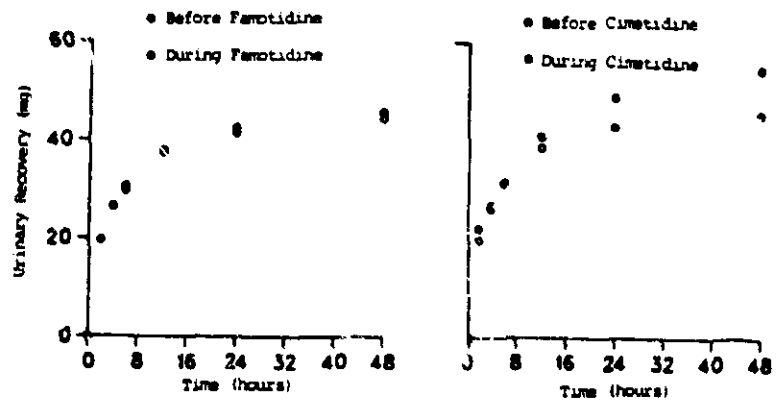


Figure 28
Cumulative Urinary Recovery of Theophylline After
I.V. Administration of 5 mg/kg Theophylline



e. Conclusion: cimetidine in therapeutic dosage, but not famotidine in higher than anticipated therapeutic dosage, decreased the metabolic elimination of theophylline.

2. Study No. 53

a. Title of study: Effect of famotidine on the anticoagulant action of sodium warfarin in healthy volunteers.

b. Investigator: Jerome R. Ryan, M.D., Clinical Research Center, New Orleans, LA.

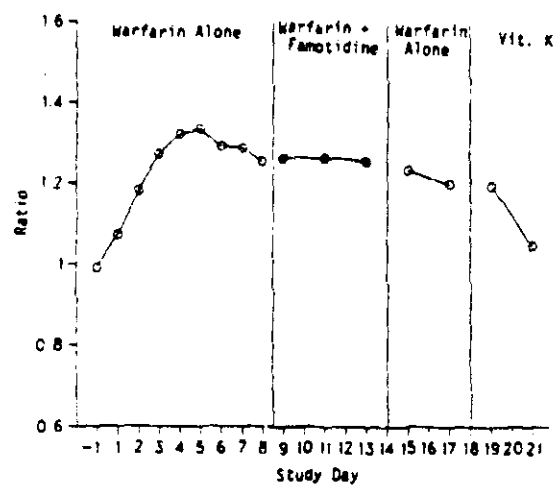
c. Design of study: 10 healthy male subjects participated. During Period I the subjects received a single-oral dose of sodium warfarin in the evening; prothrombin times (PTs) were determined in the morning. The dose of sodium warfarin was adjusted by the investigator so that the subjects were sub-therapeutically anti-coagulated, defined as a PT which was just a few seconds longer than the subject's baseline (a maximum of 2.5 x control). The subject was maintained on this dosage to insure that a steady state had been achieved, defined as PTs on 3 consecutive days within 15% of each other. During Period II the subjects received famotidine 40 mg orally morning and evening for 4.5 days, the last dose having been administered on the morning of the 5th day; the maintenance dose of sodium warfarin was continued once a day in the evening for 5 days. During Period III the subjects received their maintenance dose of sodium warfarin once a day in the evening for 5 days followed by a brief washout period during which no drug was administered. At the beginning of the washout period, subjects received a single 5 mg dose of vitamin K. The washout period lasted until the subject's PT value was within one second of the baseline. Throughout the investigation blood samples for determination for PTs were collected at intervals appropriate to the purpose of the investigation.

d. Results

(1) Safety: five subjects reported clinical adverse experiences; one (watery stool with gas) was considered possibly drug-related. The symptoms were in no instance severe and all resolved without residual effects. No subjects were discontinued because of adverse experiences. One subject had an elevation of SGPT to 71 units (ULN 45) at the end of the study; the subject was lost to follow-up.

(2) Effect on prothrombin time (figure 29): famotidine did not affect the prothrombin time in normal volunteers receiving warfarin (range 2-10 mg/day) plus famotidine 40 mg orally daily for 4.5 days.

Figure 29
Mean Prothrombine Time Ratios (N=10)



e. Conclusion: repeated administration of famotidine 40 mg b.i.d. for 4.5 days had no effect on the anticoagulant action of the sodium warfarin.

3. Study No. 55

a. Title of study: An open label, randomized, 2-way cross-over study to assess the effect of famotidine and of cimetidine on the disposition of oral phenytoin and on hepatic blood flow.

b. Investigator: Roger L. Williams, M.D., Drug Studies Unit, University of California, San Francisco, CA.

c. Design of Study: an open-label, randomized two-way cross-over study in 10 healthy volunteers, 8 men and 2 women ranging in ages from 20 to 47 years with a mean of 30.6 years, to examine the effects of repeated doses of cimetidine and of famotidine on the plasma kinetics of phenytoin given as a single oral dose and on the hepatic blood flow determined by the kinetics of indocyanine green (ICG) given intravenously. Part 1 of the study was a baseline segment consisting of 5 days in which oral phenytoin 100 mg and intravenous ICG 0.5 mg/kg were given on the morning of day 1 of the study. Blood and urine were collected for 96 hours to the morning of day 5. Part 2 was an 8-day drug-treatment period during which either famotidine 40 mg h.s. or cimetidine 300 mg q.i.d. were administered for 7 days from day 6 through day 12. Single doses of phenytoin 100 mg p.o. and ICG 0.5 mg/kg IV were given on the 3rd day of this period, i.e., day 9. Blood and urine samples were collected from the start of the phenytoin-ICG administration on study day 9 for 96 hours to the morning of study day 13. A minimum 14-day washout interval separated the 2 cross-over 13-day periods of the study. Phenytoin was given as Dilantin Capsules 100 mg p.o., ICG as a 10 second intravenous bolus.

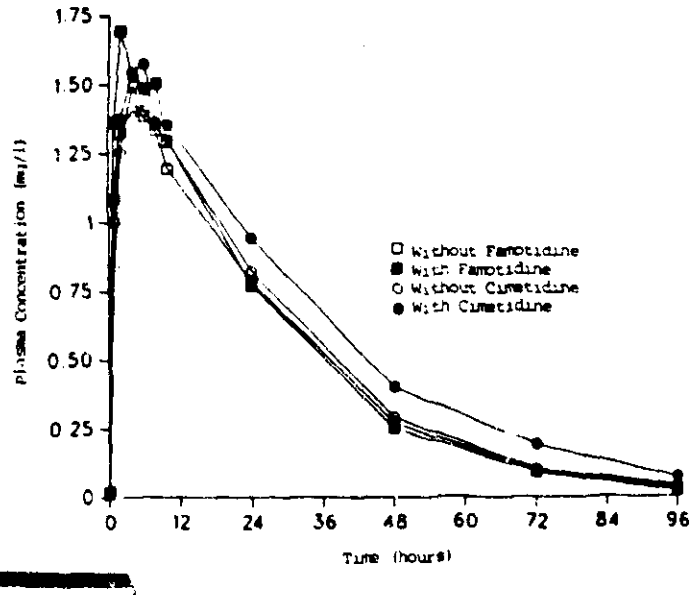
d. Results:

(1) Safety: no clinical or laboratory adverse events were reported.

(2) Pharmacokinetic observations

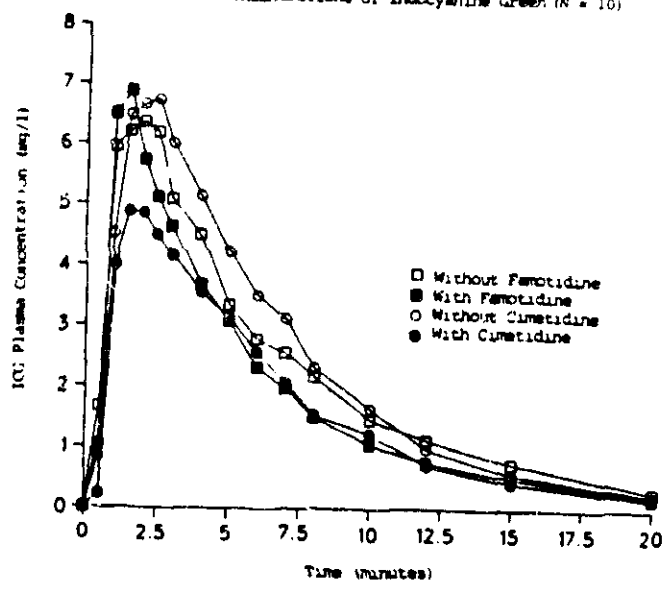
(a) Disposition of phenytoin: plasma concentrations of phenytoin were increased by concurrent administration of cimetidine but not famotidine (figure 30).

Figure 30
Mean Plasma Concentrations of Phenytoin (N = 10)



(b) Hepatic blood flow: neither drug had a significant effect on hepatic blood flow as determined by clearance of ICG (figure 31).

Figure 31
Mean Plasma Concentrations of Indocyanine Green (N = 10)



e. Conclusion: in contrast to cimetidine, famotidine does not interfere with the biological disposition of phenytoin. Neither drug appears to affect hepatic blood flow.

4. Study No. 58

a. Title of study: An open label, randomized 3-way cross-over study to assess the effects of famotidine, cimetidine and no-drug treatment on the disposition of intravenous diazepam.

b. Investigators: Miguel A. Zinny, M.D., Medical and Technical Research Associates, Needham, MA, and David A. Greenblatt, M.D., Division of Clinical Pharmacology, Tufts-New England Medical Center, Boston, MA.

c. Design of study: open, randomized, 3-way cross-over study in 13 healthy male volunteers to determine the effect of famotidine and cimetidine on the pharmacokinetics of diazepam. Each of 3 study periods lasted for 8 days. On day 2 of each period, diazepam 10 mg was given as a single intravenous infusion over 15 to 30 seconds at approximately 8 am, following which blood samples were drawn at intervals up to 168 hours. The minimum washout interval between study periods was 3 weeks. Co-administration of the test drugs began on day 1 and consisted of either famotidine 40 mg b.i.d. or cimetidine 300 mg q.i.d. for 8 days. In the other segment, no drug treatment was given in connection with the injection of diazepam.

d. Results

(1) Safety: of the 13 volunteers enrolled, one was discontinued because of abnormal liver function findings pre-study; this volunteer was replaced by another who, however, was lost to follow-up after completing the first study period (cimetidine co-administration). The remaining 11 volunteers completed the 3 study periods. The safety data from this study are combined with safety data from a previous protocol designated Study No. 56, which was the same protocol but was not suitable for analysis of effectiveness because a period of no drug treatment had not been included. Three of the subjects participating in study no. 56 had mild elevations of SGPT during both the famotidine and cimetidine periods; 4 of the subjects in protocol 58 also had mild elevations of SGPT or SGOT during both drug periods and 2 of them also had elevated SGPTs during no drug treatment. Clinical adverse experiences occurred in 2 patients receiving cimetidine but were very unlikely to be drug-related. No other adverse events were reported.

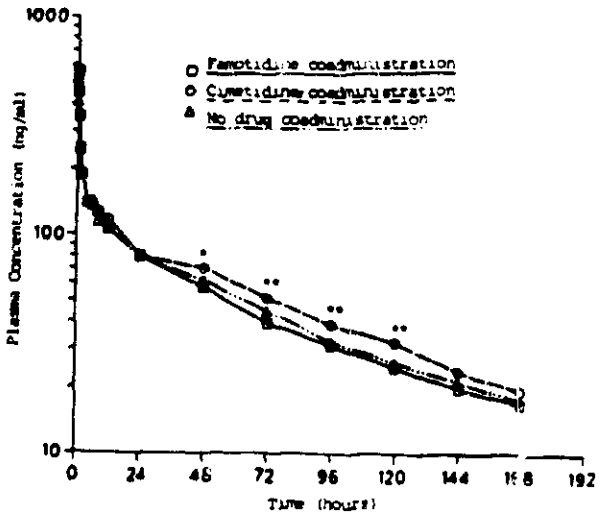
(2) Pharmacokinetics: co-administration of neither famotidine nor cimetidine influenced V_1 (apparent volume of distribution in the central compartment) or V_d (total apparent volume of distribution) of diazepam (table 4). However, cimetidine co-administration significantly prolonged the apparent diazepam elimination $t_{1/2}$ (half-life), increased AUC (total area under the plasma concentration time curve), reduced total clearance and increased the AUC of desmethyldiazepam. None of these effects were observed with co-administration of famotidine. Mean plasma concentrations of diazepam and desmethyldiazepam associated with co-administration of the respective treatments (figures 32 and 33) show that with cimetidine, but not with famotidine, there was a statistically significantly higher plasma concentration of diazepam from 24 through 120 hours and of its metabolite from 96 through 168 hours.

Table 4
Pharmacokinetic Parameters for Diazepam and Desmethyldiazepam (mean ± SD)

PARAMETER	UNITS	TREATMENT COADMINISTRATION: FAMOTIDINE	CIMETIDINE	NO DRUG
Diazepam				
V_1	liters/kg	0.21 (0.06)	0.24 (0.05)	0.26 (0.14)
V_d	liters/kg	1.08 (0.36)	1.16 (0.37)	1.17 (0.38)
$t_{1/2}$	hr	52.6 (25.5)	72.2 **(31.8)	54.7 (21.48)
Total AUC	mg/ml x hr	9.45 (3.96)	11.76 ** (3.08)	9.78 (4.11)
Clearance	ml/min/kg	0.277 (0.117)	0.201** (0.054)	0.276 (0.138)
Desmethyldiazepam				
AUC Desmethyldiazepam	mg/ml x hr	3.93 (0.78)	4.58* (1.08)	3.84 (0.79)

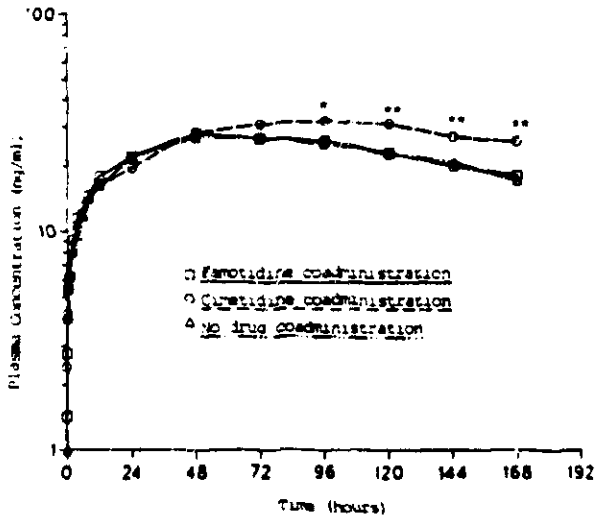
*,** Significantly different from diazepam treatment alone, $p < 0.05$, $p < 0.01$, respectively.
Note: No comparisons between MK-208 and cimetidine were performed.

Figure 32
Mean Plasma Concentrations of Diazepam (N=11)



Significantly different from diazepam treatment alone:
* p< 0.05, ** p< 0.01

Figure 33
Mean Plasma Concentrations of Desmethyldiazepam



Significantly different from diazepam treatment alone:
* p<0.05, ** p<0.01

e. Conclusion: treatment with famotidine 40 mg b.i.d., a dose higher than the recommended therapeutic dose in the treatment of peptic ulcer disease, does not alter the biological disposition of diazepam or its active metabolite desmethyldiazepam while cimetidine, in conventional therapeutic dosage, does. Thus, in contrast with what is observed with cimetidine, no problem is expected in the concurrent administration of famotidine with diazepam.

5. Study No. 690

a. Title of study: Famotidine and hepatic drug metabolism.

b. Investigators: Professor M. J. S. Langman and Dr. K. W. Somerville, Department of Therapeutics, Nottingham Medical School, Nottingham, England.

c. Design of study: open label design evaluating the effect of multiple doses of famotidine on the hepatic metabolism of 8 healthy volunteer subjects. Once during the week prior to the start of famotidine treatment and on day 7 following the morning dose of famotidine each subject received antipyrine 1 g orally, immediately following which the subjects also received ^{14}C-aminopyrine 2 microcuries as an intravenous bolus. Saliva and breath samples were obtained from each subject at specified intervals during the pre-treatment baseline and on day 7. Famotidine 40 mg was administered before breakfast and before the evening meal. Samples of saliva were assayed for antipyrine concentration as an index of plasma antipyrine concentration. $^{14}CO_2$ dpm was measured by liquid scintillation counter to indicate the hepatic demethylation of aminopyrine.

d. Results

(1) Safety: one of the 8 subjects experienced mild diarrhea throughout the 7 days on famotidine; this subsided after the investigation was completed. Two of the subjects experienced mild fatigue throughout the drug-taking phase of the investigation. One subject had a minor increase in SGPT at the end of treatment; the result of a repeat test 3 months later was normal.

(2) Hepatic drug metabolism: after 7 days of treatment with famotidine 40 mg b.i.d. the mean elimination half-life of antipyrine and aminopyrine decreased less than 10% from baseline.

e. Conclusions: the sponsor concludes, on the basis of a statistical analysis, that there is a 95% probability that the median increase from baseline levels in antipyrine half-life is less than 10% and an equal probability that the median increase in aminopyrine half-life is less than 25%.

f. Comment: in fact, one of the subjects showed an increase in the antipyrine half-life and 2 showed an increase in the aminopyrine half-life; consequently, it would appear valid to conclude that famotidine may, in some individuals, impair the oxidative metabolic functions of the liver.

6. Summary of results of studies on drug interactions: data submitted in this section are supported by a published paper (Staiger C et al, Arzneim Forsch 1984; 34:1041-1042) in concluding that famotidine does not affect oxidative metabolic functions of the liver. These observations are supported further in the results of studies showing absence of interaction of famotidine with diazepam, theophylline, phenytoin and warfarin. These data indicate that these drugs may be given without need for dosage adjustment in patients taking famotidine.

F. Ancillary studies

1. Study No. 12

a. A double-blind, dose-ranging study to evaluate the effects on healing of active duodenal ulcers with famotidine compared to placebo.

b. Investigator: Edward Cattau, Jr., M.D., National Naval Medical Center, Bethesda, MD.

c. Design of study: in the course of this clinical trial, samples of gastric secretions were obtained at the baseline endoscopy, at the end of the short-term study and at the end of 6 months (treatment was continued to evaluate prevention of recurrence). During endoscopy 5 ml of aspirate was collected in a sterile syringe for both qualitative and quantitative analysis of aerobic and anaerobic organisms.

d. Results: only 5 patients were evaluated, all during the short-term treatment period, and in only one patient was a change in gastric flora observed.

e. Conclusion: the data are insufficient to permit any conclusions regarding a possible famotidine-related effect on gastric flora.

III Clinical Trials

A. United States studies

1. Protocol No. 5006 (US multicenter trial)

a. Title of study: Famotidine in the short-term treatment of duodenal ulcer.

b. Design of the trial

(1) Admission criteria: patients with clinical symptoms of duodenal ulcer with an endoscopically demonstrated duodenal ulcer 0.5 to 2.5 cm in longest dimension.

(2) Exclusions

(a) Pyloric stenosis or peptic ulcer other than in the duodenal bulb
(b) Zollinger-Ellison syndrome
(c) Complications such as perforation or gross hemorrhage within 7 days
(d) Treatment with anticholinergics or H_2-blockers within the previous week
(e) Concomitant significant disease
(f) Lactation or child-bearing potential.

(3) Clinical observations: history of previous peptic ulcer disease, alcohol and smoking habits, physical examination, ECG, conventional clinical laboratory tests and upper endoscopy to confirm the presence of duodenal ulcer(s). Follow-up assessments of clinical symptoms were made and endoscopies performed at weeks 2, 4 and 8. Once ulcer healing was demonstrated at any of these intervals, the patients were eligible to be re-randomized into a 1 year maintenance study. Those whose ulcers had not healed at the end of 8 weeks were considered to have completed the study as a treatment failure. At each treatment visit the patients were given diary cards for daily recording of day and night pain, gastrointestinal symptoms, number of antacid tablets taken and any adverse experiences. The data from these diaries were reviewed at each visit. At the completion of the study the physical and laboratory examinations were repeated.

(4) Treatment schedules: patients were randomized to one of the following 4 dosage regimens.

(a) Famotidine 40 mg h.s. (placebo at 8:00 am, famotidine at 10:00 pm)

(b) Famotidine 20 mg b.i.d., 8:00 AM and 10:00 PM

(c) Famotidine 40 mg b.i.d., 8:00 AM and 10:00 PM

(d) Placebo at 8:00 AM and 10:00 PM

(5) Antacids: each patient received a bottle of antacid tablets to be taken only if additional symptomatic relief was required.

c. Evaluation criteria

(1) Endoscopy

(a) Normal: no ulcer present, complete epithelization of the ulcer crater, regardless of the persistence or emergence of duodenitis and/or erosions.
(b) Ulcer: incomplete epithelization of the ulcer.

(2) Pain: severity of day and night pain was recorded by the patient on a scale of 0 = none, 1 = mild, 2 = moderate and 3 = severe. The terms were not defined.

(3) Patients' assessments of global response to therapy were graded 0 = none, 1 = poor, 2 = fair and 3 = good and 4 = excellent, again without definition of the terms.

(4) Safety: adverse clinical and laboratory events were recorded and evaluated by the investigator as to severity, seriousness, relationship to study drug and outcome.

d. Statistical treatment: the analysis of effectiveness at each time point was done as an "end point" analysis, i.e., patients whose ulcers healed at weeks 2 or 4 actually completed the study per protocol and subsequently did not have data. The specific methods of analysis of the data are indicated in the tabulations of the results. Validity of the statistical methods applied by the sponsor in this and subsequent trials is the subject of a separate review of this NDA by FDA biometricians.

e. Investigators (table 5): all of the physicians participating in this clinical trial are well-qualified by training and experience to undertake studies of this type.

Table 5

Name/Study No.	Affiliation	Location
Elliot Alpert, M.D./43	Methodist Hospital	Houston, Texas 77030
Robert H. Bishop, Jr.,M.D./10	3246 N. Meridian Street	Indianapolis, IN 46208
James M. Butt III, M.D./11	Veterans Administration Hospital	Columbia, MO 65212
James Campbell, M.D./22	University of Nebraska Med.Ctr.	Omaha, Nebraska 68105
Edward L. Cattau, Jr., M.D./12	National Naval Medical Center	Bethesda, Maryland 20014
William Erdel, M.D./16	St. Vincent's Hospital	Indianapolis, IN 46260
Norman Gitlin, M.D./13	Veterans Admin. Hospital	Fresno, CA 93703
Daniel Pelot, M.D./14	University of California	Irvine, CA 92717
Shahanawaz Jaffer, M.D./19	Hagan Medical Clinical Inc.	Covina, CA 91723
James M. Johnson, M.D./17	Watson Clinic	Lakeland, FLA 33801
R. Bruce Johnson, M.D./15	Rees-Stealy Medical Group	San Diego, CA 92101
James F. King, M.D./18	Gastroenterology Associates	Canton, Ohio 44708
Stephen M. Levine, M.D./35	1210 Brace Road	Cherry Hill, NJ 08034
Ross Madden, M.D./49	Medical Associates Clinic, P.C.	Dubuque, Iowa 52001
Arthur J. McCullough, Jr., M.D./44	Metropolitan General Hospital	Cleveland, Ohio 44109
Frank Miao, M.D./24	Fullerton Internal Medicine Clinic	Fullerton, CA 92635
William A. Millson, M.D./23	3730 Olentangy River Road	Columbus, OH 43214
Richard Redinger, M.D./25	University of Louisville	Louisville, KY 40202
Allen Rubin, M.D./21	5959 Harry Hines Blvd.	Dallas, TX 75235
Ivan Rudolph, M.D./26	Brachfeld Medical Associates	Willingboro, NJ 08046
Cesar Rudzki, M.D./46	Washington Center for Clinical Studies	Washington, DC
Ram Shrivastava, M.D./31	Eastside Comprehensive Medical Services	New York, NY 10021
J. Lacey Smith, M.D./28	Veterans Admin. Medical Center	Houston, TX 77211
Joseph Spear, M.D./37	6004 Ventnor Ave.	Ventnor City, NJ 08406
E.Clinton Texter,M.D./29	Univ. of Arkansas for Medical Sciences	Little Rock, AR 72205
Joycelyn Theard, M.D./45	San Antonio Center for Clinical Studies	San Antonio, TX 78212
Fred B. Thomas, M.D./09	Ohio State University	Columbus, OH 43210
Ronald Thune, M.D./50	West Side Clinic, S.C.	Green Bay, WI 54303
Jorge Valenzuela, M.D./38	U.S.C. Medical Center	Los Angeles, CA 90033
Stephen D. Ward, M.D./34	1245 Highland Ave.	Abington, PA 19001
Robert W. Lufkin, M.D./30	Florida Center for Clinical Studies	St.Petersburg, FL 33701
Dominic Wong, M.D./27	Henry Ford Hospital	Detroit, MI 48202
Herbert A. Yantes, M.D./57	Phila. Center for Clinical Studies	Philadelphia, PA 19152
Alvin M. Zfass, M.D./32	Medical College of Virginia	Richmond, VA 23298

f. Results

(1) Comparability of treatment groups (table 6): the 4 treatment groups were comparable in all essential characteristics.

TABLE 6

Comparability of Treatment Groups, number %

	FAMOTIDINE 40 HS (n=96)	FAMOTIDINE 20 BID (n=89)	FAMOTIDINE 40 BID (n=95)	Placebo (n=100)
Age				
Mean	45.6	47.3	43.6	46.4
Sex				
Males	75 (78)	69 (78)	81 (82)	76 (76)
Females	21 (22)	20 (22)	18 (18)	24 (24)
Weight (lb.)	167.9	171.9	[illegible]	166.5
Smoking	58 (60)	52 (58)	59 (60)	61 (61)
Alcohol	18 (19)	12 (13)	14 (14)	13 (13)
Caffeine	56 (58)	59 (66)	62 (63)	59 (59)
Initial Ulcer Size (cm)[a]				
Mean	0.86	0.91	0.88	0.86
Number of Ulcers				
One	79 (82)	73 (82)	88 (89)	82 (87)
Two or more	17 (18)	16 (18)	11 (11)	13 (13)
Age at First Ulcer				
Mean	37.9	40.6	35.8	39.7
Duration of Ulcer Hx (yrs)				
Mean	7.7	6.7	7.8	6.7
Ulcer History				
None	30 (31)	42 (47)	34 (34)	26 (26)
Single	22 (23)	19 (21)	24 (24)	30 (30)
Multiple	44 (46)	28 (31)	41 (42)	44 (44)
Other pathology in esophagus	24 (25)	27 (30)	20 (20)	33 (33)
Other pathology in stomach	32 (33)	26 (29)	32 (32)	31 (31)
Other pathology in duodenum	62 (66)	50 (56)	61 (62)	63 (63)
Concomitant diseases				
Cardiovascular	7 (7)	9 (10)	11 (11)	7 (7)
Respiratory	4 (4)	4 (4)	6 (6)	3 (3)
Gastrointestinal	9 (9)	10 (11)	9 (9)	13 (13)
Musculoskeletal	6 (6)	10 (11)	6 (6)	2 (2)
Endocrine	5 (5)	2 (2)	5 (5)	8 (8)
Other	4 (4)	7 (8)	7 (7)	7 (7)

[a]For patients with more than one ulcer, this was the size of the largest ulcer. No significant differences were observed.

(2) Safety

(a) Vital signs (table 7): there was a statistically significant decrease in the mean pulse rate in patients receiving 40 mg b.i.d. and in the mean systolic blood pressure in patients receiving 40 mg h.s; these changes are not, however, of any clinical significance.

TABLE 7

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE FROM BASELINE
Pulse rate (beats/min.)	40 HS	94	75.9	74.5	-1.3
	20 BID	86	76.7	75.4	-1.3
	40 BID	95	76.8	73.0	-3.8+,**
	Placebo	97	76.1	76.7	0.6
Systolic BP (mmHg)	40 HS	96	122.4	119.5	-2.9*
	20 BID	87	123.5	124.8	1.3
	40 BID	95	123.1	123.5	0.4
	Placebo	97	125.0	123.3	-1.7
Diastolic BP (mmHg)	40 HS	96	77.3	76.9	-0.4
	20 BID	87	77.4	78.2	0.8
	40 BID	95	78.7	78.4	-0.3
	Placebo	97	77.6	78.0	0.4
Weight (lbs.)	40 HS	91	167.9	168.5	0.6
	20 BID	83	171.9	172.1	0.2
	40 BID	91	170.1	170.1	-0.1
	Placebo	89	166.5	167.0	0.5

*,**Significant change from baseline, $p \leq .05$, $p \leq .01$, respectively.
+Significantly different from placebo, $p \leq .01$.

(b) Laboratory adverse events: in patients on famotidine there were no serious abnormal laboratory values; no patient receiving famotidine was withdrawn because of an adverse laboratory event. The one patient with a laboratory finding considered serious was on placebo.

(c) Clinical adverse experiences: the percentage of patients with adverse signs/symptoms (table 8) regardless of drug-relationship was no greater with famotidine treatment (27%) than with placebo (39%). The incidence of adverse experiences in patients 60 years or older was not different from that in the general population.

TABLE 8

Number Of Patients With Clinical Adverse Events (%)*

BODY SYSTEM	Famotidine 40 HS N = 96	Famotidine 20 BID N = 89	Famotidine 40 BID N = 99	PLACEBO N = 100
Central Nervous System				
Dizziness	0	3 (3)	1 (1)	4 (4)
Fatigue	1 (1)	2 (2)	1 (1)	1 (1)
Headache	5 (5)	8 (9)	9 (9)	11 (11)
Insomnia	0	2 (2)	0	2 (2)
Nervousness	0	1 (1)	2 (2)	2 (2)
TOTAL	6 (6)	16 (18)	13 (13)	20 (20)
Cardiovascular				
Thrombo- or phlebitis	0	0	2 (2)	4 (4)
Digestive				
Abdominal Pain	0	1 (1)	0	2 (2)
Anorexia	2 (2)	1 (1)	2 (2)	0
Constipation	3 (3)	1 (1)	2 (2)	1 (1)
Diarrhea	2 (2)	3 (3)	1 (1)	5 (5)
Dyspepsia	2 (2)	0	1 (1)	0
Flatulence	2 (2)	0	0	2 (2)
G.I. Hemorrhage	4 (4)	0	0	1 (1)
Nausea	2 (2)	1 (1)	0	3 (3)
TOTAL	17 (18)	7 (8)	6 (6)	14 (14)
Respiratory System				
Common Cold	0	3 (3)	0	0
Cough	0	2 (2)	0	0
Pharyngeal Pain	0	2 (2)	0	1 (1)
TOTAL	0	7 (6)	0	1 (1)
Tegumentary				
Hyperhydrosis	0	0	2 (2)	0
TOTAL	23 (24)	30 (34)	23 (23)	39 (39)

*Adverse experiences with an incidence of at least 2% in at least one of the treatment groups are displayed in this table

A more meaningful analysis lists the patients withdrawn from treatment because of adverse signs/symptoms (table 9); here the incidence seems appreciable (2-3% on drug, 5% on placebo) but many of these adverse occurrences represent complications of the underlying peptic ulcer disease. In evaluating the possible drug-relationship of these occurrences I have chosen to classify the sponsor's "probably not" as "possibly yes". Even with this "strict construction" it is clear that in this clinical trial famotidine appears to be a relatively safe drug.

TABLE 9

Patients Withdrawn because of Adverse Signs/Symptoms

TREATMENT	ALLOC	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	TOTAL POSSIBLY/PROB DRUG-RELATED
Famotidine 40 HS	1218	Gastric Ulcer	Severe	Probably not[a]	
		Hematemesis	Severe	Probably not	
	1216	Herpes Zoster	Severe	Probably not	
	1635	G.I. Hemorrhage	Severe	Def. not	
		Hematemesis	Severe	Def. not	
		Syncope	Severe	Def. not	
	1604	G.I. Hemorrhage	Moderate	Possibly	3/96 (3%)
Famotidine 20 BID	1267	Gastric Ulcer	Mild	Possibly	
	1539	Asthma	Severe	Probably not	
	1576	G.I. Pain	Moderate	Probably not	
		Nausea	Moderate	Probably not	
		Vomiting	Moderate	Probably not	3/89 (3%)
Famotidine 40 BID	1099	Grand mal Seizures	Severe	Possibly	
	1050	Conjunctival Inj.	Mild	Probably	
		Orbital Edema	Mild	Probably	2/99 (2%)
PLACEBO	1521	Vomiting	Severe	Def. not	
	1123	Chest Pain	Moderate	Probably not	
	1432	Gastric Ulcer	Mild	Possibly	
	1126	Headache	Mild	Possibly	
		Nausea	Mild	Possibly	
		Vomiting	Mild	Possibly	
	1215	Asthenia	Moderate	Possibly	
		Headache	Mild	Possibly	
		Abdominal Swelling	Moderate	Possibly	
		Constipation	Moderate	Possibly	
	1875	Gastric Ulcer	Mild	Possibly	5/100 (5%)

[a] "Probably not" = "Possibly yes"

(3) Effectiveness

(a) Number of patients evaluable: patients omitted from analysis of effectiveness (table 10) were remarkably few (22/384, 6%) considering the large number of patients entered in each treatment group. These non-cooperative patients or investigators (protocol violations, off drug) were identified early in the trial so that very few were lost after week 2. As might be expected, discontinuation because of ineffective therapy was highest in the placebo group (13%), but less expected was the high incidence (8%) of discontinuation because of adverse experiences.

Table 10
Number of Patients in Analysis of Results

	WEEK 2				WEEK 4				WEEK 8			
	Famotidine				Famotidine				Famotidine			
	40 HS	20 BID	40 BID	PBO	40 HS	20 BID	40 BID	PBO	40 HS	20 BID	40 BID	PBO
Total Entered	96	89	99	100	96	89	99	100	96	89	99	100
Patients with Incomplete Data												
Discontinued Adverse Experience	3	2	1	2	3	2	2	7	4	3	2	8
Discontinued Ineffective Therapy	0	1	1	6	1	1	1	10	1	1	1	13
Discontinued Other	3	3	3	4	5	4	8	10	5	4	8	10
Protocol Violations[b]	4	4	6	3	4	4	6	3	4	4	6	3
Off Drug[b]	2	0	0	0	3	1	0	0	3	1	0	0
No Treatment Data[c]	4	3	5	0	3	2	5	0	3	2	5	0
Total Included[a]												
Ulcer Healing	90	85	93	97	89	84	93	97	89	84	93	97
Day/Night Pain	86	82	88	97	86	82	88	97	86	82	97	86

[a] Patients who dropped out, were out of range, etc. had their last valid values carried forward to subsequent timepoints.
[b] Not included in per protocol ulcer healing and day/night pain analysis.
[c] Not included in per protocol day/night pain analysis.

(b) Incidence of healing: the sponsor tabulates the incidence of healing at weeks 2, 4 and 8; week 2 included endoscopies performed up to 18 days on treatment, week 4 up to 34 days and week 8 up to 65 days. The results (table 11) leave no doubt that all three doses of famotidine yield a similar incidence of healing and all are significantly more effective than placebo.

Table 11
Cumulative Number Healed/Number in Treatment Group (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=89	Famotidine 20 BID N=84	Famotidine 40 BID N=93	Placebo N=97
2 (Days 1-28)	28 (32)	32 (38)	31 (33)	16 (17)
4 (Days 19-34)	62 (70)	56 (67)	69 (74)	30 (31)
8 (Days 35-64)	74 (83)	69 (82)	75 (81)	44 (45)
Beyond Week 8 (Days 65-85)	75 (84)	69 (82)	76 (82)	44 (45)

At each time point, each of the famotidine treatment groups had a significantly higher healing rate than placebo, p<.001.

Since, however, demonstration of healing after 34 days of treatment is manifestly not proof of healing within 4 weeks, I requested the sponsor to tabulate the incidence of healing by actual weeks. This tabulation (table 12) shows that if the first follow-up endoscopy is performed at 5 weeks, a significantly smaller percentage of patents will require further treatment and an additional endoscopy. With the recommended dose (40 mg h.s.) the incidence of healing at 5 weeks was 70% compared to 53% at 4 weeks; with 40 mg b.i.d., the incidence of healing at 5 weeks was 75% compared to 54% at 4 weeks.

TABLE 12

Cumulative Number Healed (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=89	Famotidine 20 BID N=84	Famotidine 40 BID N=93	Placebo N=97
Week 1 (Days 2-8)*	0 (0)	0 (0)	0 (0)	0 (0)
Week 2 (Days 9-15)	21 (24)	25 (30)	20 (22)	8 (8)
Week 3 (Days 16-22)	31 (35)	35 (42)	32 (34)	16 (16)
Week 4 (Days 23-29)	47 (53)	49 (58)	50 (54)	24 (25)
Week 5 (Days 30-36)	62 (70)	57 (68)	70 (75)	30 (31)
Week 6 (Days 37-43)	62 (70)	59 (70)	70 (75)	30 (31)
Week 7 (Days 44-50)	63 (71)	59 (70)	70 (75)	30 (31)
Week 8 (Days 51-57)	70 (79)	62 (74)	72 (77)	39 (40)

* Day 1 was the day of the baseline evaluation. Patients started taking drug at bedtime on day 1. All weekly day ranges start with day 2.

Among the 5 investigators who contributed at least 20 patients there was generally not much treatment-by-investigator interaction (table 13) except as regards placebo incidence of healing which varied from 10 to 60% at 4 weeks, 33-80% at 8 weeks. This is not a novel observation.

TABLE 13

Number (%) Healing Reported by Investigators with at Least 20 Patients --Number (%) Healed

Inv.	FAMOTIDINE 40 HS N	WK 2	WK 4	WK 8	FAMOTIDINE 20 BID N	WK 2	WK 4	WK 8	FAMOTIDINE 40 BID N	WK 2	WK 4	WK 8	PLACEBO N	WK 2	WK 4	WK 8
1	6	0 (0)	1 (17)	6(100)	4	2 (50)	3 (75)	3 (75)	5	2 (40)	4 (80)	5(100)	5	1 (20)	3 (60)	4 (80)
2	7	2 (29)	5 (71)	5 (71)	7	2 (29)	3 (43)	5 (71)	6	3 (50)	5 (83)	5 (83)	7	2 (29)	3 (43)	3 (43)
3	10	3 (30)	5 (50)	5 (50)	6	4 (50)	5 (63)	6 (75)	9	0 (0)	8 (89)	9(100)	10	1 (10)	1 (10)	6 (60)
4	8	4 (50)	8 (100)	8(100)	9	3 (33)	5 (56)	5 (56)	6	1 (17)	3 (50)	3 (50)	9	1 (11)	2 (22)	4 (44)
5	7	4 (57)	6 (86)	7(100)	8	3 (38)	7 (88)	8(100)	7	5 (71)	7(100)	7(100)	9	3 (33)	3 (33)	3 (33)
SUBTOTAL	38	13 (34)	25 (66)	31 (82)	36	14 (33)	23 (64)	27 (75)	33	11 (33)	27 (82)	29 (88)	40	8 (20)	12 (30)	18 (45)
*Pool	51	15 (24)	37 (73)	43 (84)	48	18 (38)	33 (69)	42 (88)	60	20 (33)	42 (70)	46 (77)	57	8 (14)	18 (32)	26 (46)
TOTAL	89	28 (32)	62 (70)	74 (83)	84	32 (38)	56 (67)	69 (82)	93	31 (33)	69 (74)	75 (81)	97	16 (16)	30 (31)	44 (45)

*All Other Investigators Combined.

(c) Effect of treatment on duodenitis/erosions: duodenitis and/or erosions co-existed with the duodenal ulcers in 201/363 (55%) of patients in whom such information was available at the pre-treatment endoscopy. Some observers consider the presence of duodenitis and/or erosions part of the spectrum of peptic ulcer disease. It is therefore of interest to evaluate the effect of treatment on these lesions and any effect their presence may have on ulcer healing (table 14). Among patients in whom the endoscopic records included reports of the presence or absence of duodenitis and/or erosions both before and after treatment in the same patients, the post-treatment incidence of duodenitis and/or erosions in patients in whom these lesions were not present pre-treatment was 24/78 (31%) on famotidine, 11/32 (34%) on placebo; the emergence of these lesions during treatment had no effect on healing of the ulcers. In patients in whom duodenitis and/or erosions were present pre-treatment, such lesions persisted in 84/146 (58%) on drug, 38/54 (72%) on placebo; the persistence of these lesions had no effect on the healing of the ulcers.

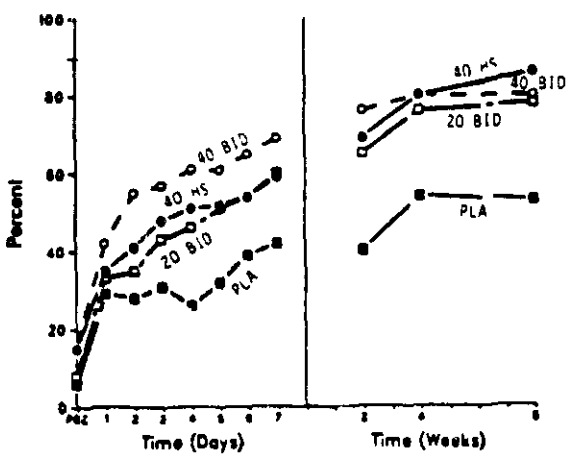
TABLE 14

Effect of Treatment on incidence of duodenitis/erosions and relation to healing of ulcer

	Duodenitis and/or erosions post-treatment and percent ulcers healed																	
	FAMOTIDINE												TOTAL				PLACEBO	
Duodenitis/ erosions pre-treatment	N	%	Ulcer Healed	%	N	%	Ulcer Healed	%	N	%	Ulcer Healed	%	N	%	Ulcer Healed	%	N	%	Ulcer Healed	%
None	11/24	46	11/11	100	6/28	21	5/6	83	7/26	27	7/7	100	24/78	31	23/24	96	11/32	34	6/11	36
Duodenitis/ erosions	32/63	51	26/32	81	26/43	60	21/26	81	26/51	51	23/26	88	84/143	58	70/84	83	39/54	72	19/39	49
TOTAL	43/87	49	37/43	86	32/71	45	26/32	81	33/77	43	30/33	91	108/225	48	93/108	86	50/86	58	23/50	46

(d) Relief of pain: the proportion of patients relieved of day pain was higher at all time points from the 3rd day onward through 8 weeks with all doses of famotidine than with placebo (figure 34). The proportion of patients relieved of night pain at the end of the first week was higher with the 40 mg h.s. and 40 mg b.i.d. doses than with 20 mg b.i.d. or placebo; from the second week onward, proportionately more patients receiving any dose of famotidine were relieved of night pain than were those receiving placebo (figure 35). The median number of days to relief of pain was significantly fewer with all doses of famotidine than with placebo (table 15).

Figure 34
Percentage of Patients With No Day Pain



Percentage of Patients With No Night Pain

Figure 35
Percentage of Patients With No Night Pain

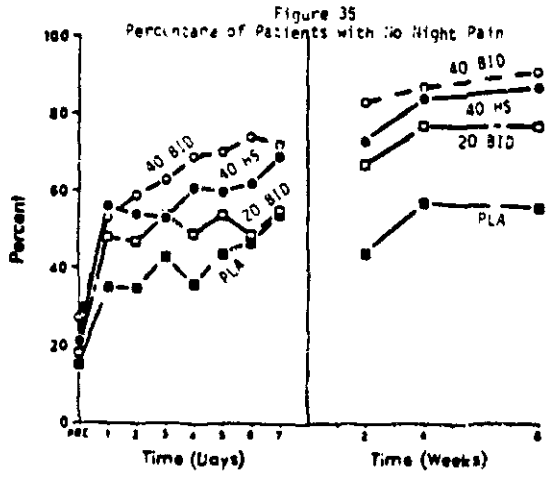


Table 15
Incidence, and Median Time to, Relief of Pain (Days)

		FAMOTIDINE 40 HS (n = 89)	20 BID (n = 84)	40 BID (n = 93)	PLACEBO (n = 97)
	Day Pain				
Incidence (%)		76 (85)	77 (92)	78 (84)	91 (94)
Baseline =	None[a]	10 (n = 13)	1 (n = 7)	13 (n = 15)	22 (n = 6)
	Mild	6 (n = 23)	13 (n = 18)	4 (n = 25)	64 (n = 29)
	Moderate	14 (n = 35)	14 (n = 36)	10 (n = 39)	55 (n = 37)
	Severe	12 (n = 18)	20 (n = 23)	10.5 (n = 14)	27 (n = 25)
	Total	11 (n = 89)	14.5 (n = 84)	9 (n = 93)	54 (n = 97)
	Night Pain				
Incidence (%)		76 (85)	68 (81)	65 (70)	82 (85)
Baseline =	None[a]	6.5 (n = 13)	6.5 (n = 16)	2 (n = 27)	11 (n = 15)
	Mild	10 (n = 21)	16 (n = 16)	2 (n = 17)	34.5 (n = 20)
	Moderate	9 (n = 33)	21 (n = 29)	9.5 (n = 28)	64 (n = 33)
	Severe	19 (n = 15)	11 (n = 23)	22 (n = 20)	54 (n = 29)
	Total	10 (n = 89)	14.5 (n = 84)	5.5 (n = 92)	52 (n = 97)

[a] Some patients had no pain at baseline but had pain at one or more subsequent timepoints. A significant within-group change from baseline was observed for each treatment group, $p<.01$. For both relief of Day Pain and relief of Night Pain, each of the famotidine groups were significantly better than placebo, $p < .001$.

(e) Antacid consumption: throughout most of the 8 weeks of the trial, the percentage of patients taking antacids was higher in the placebo-treated than in the famotidine-treated patients (figure 36). The mean number of days of antacid therapy (table 16) and the mean number of antacid tablets taken daily (table 17) were statistically significantly fewer at most intervals with famotidine than with placebo, but the differences were not clinically significant. For example, patients on placebo took less than one antacid tablet per day fewer throughout the 8 weeks of treatment than did the patients receiving famotidine 40 mg h.s., the dose recommended for the short-term treatment of duodenal ulcer. The mean number of days in which patients took antacids was less than one day more over an 8 week period with placebo than with the 40 mg h.s. dose.

Figure 36
Percentage of Patients Receiving Antacid Therapy

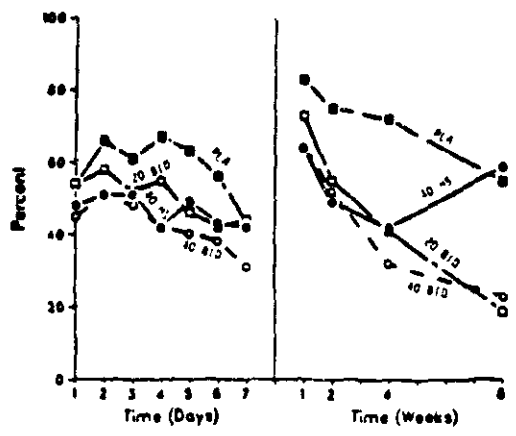


TABLE 16

Mean Days of Antacid Therapy, Mean ± Standard Deviation

	Famotidine 40 HS		Famotidine 20 BID		Famotidine 40 BID		Placebo		Number of Days Difference Between 40 HS & Placebo
WEEK	N	MEAN	N	MEAN	N	MEAN	N	MEAN	
1	97	3.3 ± 1.06	84	3.5 ± 2.80	93	2.9 ± 2.86**	98	4.1 ± 2.64	-0.8
2	87	2.7 ± 3.05**	80	2.5 ± 2.81**	84	2.0 ± 2.53**	95	3.6 ± 2.79	-0.9
4	56	2.2 ± 2.87**	45	1.9 ± 2.69**	51	1.3 ± 2.28**	70	3.3 ± 2.67	-1.1
8	21	2.9 ± 2.98	18	1.0 ± 2.22**	12	0.8 ± 1.42**	37	2.8 ± 2.89	+0.1

** Significantly different from placebo, $p \leq .01$.
+ Significantly different from 20 BID, $p \leq .05$ and significantly different from 40 BID, p .05.

TABLE 17

Number of Antacid Tablets Taken Daily, Mean ± Standard Deviation

	Famotidine 40 HS		Famotidine 20 BID		Famotidine 40 BID		Placebo		Difference Between 40 HS & Placebo
Week	N	Mean	N	Mean	N	Mean	N	Mean	
1	92	1.7±2.15**	84	1.9±2.35	93	1.5±2.15**	98	2.2±2.05	-0.5
2	87	1.4±1.99**	80	1.2±1.90**	84	0.9±1.51**	95	2.1±2.34	-0.9
4	56	1.0±1.71**	45	1.0±1.97**	51	0.6±1.23**	70	1.7±1.94	-0.7
8	21	1.2±1.41	18	0.7±2.13**	12	0.3±0.71*	37	1.4±1.79	-0.2

*,** Significantly different from placebo, $p \leq .05$, $p \leq .01$, respectively.

(g) Summary: this trial of the short-term (up to 8 weeks) healing of duodenal ulcer compared famotidine in doses of 40 mg h.s., 20 mg b.i.d. and 40 mg b.i.d. with placebo in a total of 384 patients of whom 366 were evaluable for effectiveness. Healing, defined as complete re-epithelization of the ulcer site regardless of the persistence or emergence of duodenitis and/or erosions, was evaluated at 2, 4 and 8 weeks, depending on the interval at which the ulcer was found to be healed.

The incidence of healing was highly significantly better than placebo with all doses at all treatment weeks (p 0.001). With the doses of 40 mg h.s., 20 mg b.i.d, 40 mg b.i.d. and placebo, the crude incidence of healing of ulcer was 83%, 82%, 82% and 45% respectively. The respective percentages as calculated by life-table analysis were 88%, 89%, 89% and 55%.

The drug groups showed significant reduction in day and night pain compared to placebo (p 0.001) and in the consumption of antacids. However, the differences between famotidine and placebo in the amount of antacid consumed and the number of days antacid were taken was not clinically significant.

The most common clinical adverse experiences were headache (5.2%) and constipation (3.1%) in the group receiving 40 mg h.s. as contrasted with respective incidences of 11.0% and 1.0% in the placebo group. Eight of 284 patients (3%) receiving famotidine and 5 of the 100 receiving placebo (5%) were withdrawn because of clinical adverse experiences.

Serious clinical adverse experiences reported during the study were either complications of pre-existing conditions or were the result of treatment failure. Serious laboratory adverse experiences were no more frequent in the famotidine groups than in the placebo group.

Based on the results of this study the sponsor recommends a 40 mg h.s. dosage regimen for the short-term therapy of duodenal ulcer.

2. Protocol number: none assigned

a. Title of study: famotidine in the prevention of recurrence of duodenal ulcer.

b. Design of study: double-blind, randomized, multi-center, placebo-controlled dose-ranging study. Patients who had a healed ulcer in the short-term treatment period were invited to enter this (maintenance) phase of the study. The patients were re-randomized to treatment with either famotidine 40 or 20 mg h.s. or placebo. Patients were re-endoscoped after 4 weeks (up to 42 days on treatment), 12 weeks (days 43-105) and 24 weeks (day 106 and later), unless symptomatic relapse called for endoscopic examination before the scheduled return visit.

c. Investigators: twenty-four of the 34 investigators who participated in the short-term trial participated in this trial. Fifteen of the investigators contributed 5 or fewer patients, while only 7 contributed 10 or more. The success of the investigators in enrolling eligible patients into the long-term trial varied over a considerable range from 55 to 88%.

d. Results

(1) Comparability of the patient groups: 54 patients were allocated to 40 mg h.s., 57 to 20 mg h.s. and 66 to placebo. The treatment groups were comparable in all essential respects (table 18).

TABLE 18

Comparability of Treatment Groups

	FAMOTIDINE 40 HS (N=54)	FAMOTIDINE 20 HS (N=57)	PLACEBO (N=66)
Age (Years), Mean	50.6**	46.6	43.3
Sex			
Females	14 (26%)	15 (26%)	17 (26%)
Males	40 (74%)	42 (74%)	49 (74%)
Treatment in Acute Study			
Famotidine 40 HS	14 (26%)	18 (32%)	17 (26%)
Famotidine 20 BID	16 (30%)	15 (26%)	12 (18%)
Famotidine 40 BID	15 (28%)	16 (28%)	22 (33%)
Placebo	9 (17%)	7 (12%)	15 (23%)
Week Ulcer Healed in Acute Study			
Week 2	29 (54%)[a]	26 (46%)	25 (38%)
Week 4	20 (37%)	20 (35%)	31 (47%)
Week 8 or Later	5 (9%)	11 (19%)	10 (15%)
Smoking	31 (57%)	40 (70%)	42 (64%)
Drinking	12 (22%)	8 (14%)	14 (21%)
Initial Ulcer Size, Mean	0.82	0.89	0.92
Number of Ulcers			
One	42 (78%)	49 (86%)	60 (91%)
Two or More	12 (22%)	8 (14%)	6 (9%)
Age at First Ulcer (Years), Mean	43.5**,+	37.7	36.1
Duration of Ulcer Disease (Years), Mean	7.0	8.8	7.3
Ulcer History			
None	25 (46%)	21 (37%)	21 (32%)
One Previous Episode	17 (31%)	22 (39%)	24 (36%)
Multiple Previous Episodes	12 (22%)	14 (25%)	21 (32%)
Other Pathology in Esophagus	13 (25%)	13 (23%)	19 (29%)
Other Pathology in Stomach	13 (25%)[b]	7 (12%)	9 (14%)
Other Pathology in Duodenum	30 (57%)	30 (53%)	30 (45%)

*,** Significantly different from placebo group, $p<0.05$, $p<0.01$ respectively.
+ Significantly different from famotidine 20 HS group, $p<0.05$.
a,b Different from Placebo group, $p=0.08$, $p=0.10$ respectively.

(2) Exclusions from analysis for effectiveness (table 19): the most frequent reason for exclusion was failure to take the prescribed medication for various periods of time at various intervals of the trial. The proportion of patients excluded from the analysis for effectiveness of 40 mg h.s., 20 mg h.s. and placebo was respectively 9%, 14% and 6% which is not a bad record for a 6 month trial. In addition to these exclusions a number of patients dropped out at at various intervals during the trial for various reasons; the sponsor's accounting for these patients is a matter to be addressed by our biometricians.

TABLE 19

Exclusions from Analysis of Effectiveness

	Treatment		
	40 HS N = 54	20 HS N = 57	PLA N = 66
Off drug[a]	3	4	4
Off drug[b]	1	2	0
Off drug[c]	0	1	0
Protocol deviation	1	1	0
Total	5 (9%)	8 (14%)	4 (6%)
Included in analysis for effectiveness	49	49	62

a More than 7 consecutive days
b More than 5 days during weeks 1-4
c More than 10 days during weeks 5-12

(3) Safety

(a) Vital signs (table 20): the only statistically significant change from baseline was an increase in mean systolic BP from 121.7 to 126.1 in patients receiving 20 mg h.s. It is doubtful whether this has any clinical importance.

TABLE 20

Effect of Treatment on Vital Signs, Mean Values

Measurement	Treatment Group	N	Baseline	Endpoint	Change From Baseline
Body Weight (lbs)	Famotidine 40 HS	15	174.0	172.3	-1.7
	Famotidine 20 HS	11	171.6	172.3	0.6
	Placebo	34	168.0	168.3	0.2
Pulse (beats/min)	Famotidine 40 HS	54	71.7	72.0	0.2
	Famotidine 20 HS	52	74.6	73.5	-1.1
	Placebo	64	72.9	75.8	2.9[B]
Systolic Blood Pressure (mmHg)	Famotidine 40 HS	54	121.6	122.2	0.6
	Famotidine 20 HS	52	121.7	126.1	4.4*,+
	Placebo	65	123.3	120.9	-2.4
Diastolic Blood Pressure (mmHg)	Famotidine 40 HS	54	76.5	76.1	-0.4
	Famotidine 20 HS	52	79.1	79.4	0.3
	Placebo	65	76.3	77.6	1.3

* Significantly different from placebo group, $p < .05$.
\+ Significant change from baseline, $p < .05$.
B Change from baseline, $0.05 \leq p \leq 0.10$.

(b) Clinical adverse experiences: the incidence of adverse signs/symptoms was similar in the 3 groups (40 h.s. 23%, placebo 29%). The number withdrawn because of adverse experiences was no greater with famotidine (4/111, 4%) than with placebo (6/66, 10%).

Adverse clinical experiences classified by body system (table 21) or by symptoms (table 22) were generally no more frequent in patients receiving famotidine than in those receiving placebo.

TABLE 21

Clinical Adverse Experiences

Body System	Famotidine 20 HS (N = 57)	Famotidine 40 HS (N = 54)	Placebo (N=66)
Body as a whole	0	2 (3.7%)	1 (1.5%)
Central nervous	5 (8.8%)	6 (11.1%)	7 (10.5%)
Cardiovascular	0	1 (1.9%)	0
Digestive	6 (10.5%)	7 (13.0%)	11 (16.7%)
Respiratory	3 (5.3%)	3 (5.6%)	5 (7.6%)
Tegumentary	2 (3.5%)	1 (1.9%)	3 (4.5%)
Musculoskeletal	4 (7.0%)	2 (3.7%)	1 (1.5%)
Special Senses	1 (1.8%)	1 (1.9%)	1 (1.5%)
Urogenital	1 (1.8%)	2	0

TABLE 22

Clinical Adverse Experiences with 12% Incidence

	Famotidine 20 HS N = 57	Famotidine 40 HS N = 54	Placebo N = 66
Abdominal Pain	3 (5.3%)	3 (5.6%)	4 (6.1%)
Headache	2 (3.5%)	4 (7.4%)	4 (6.1%)
Constipation	2 (3.5%)	1 (1.9%)	2 (3.0%)
Back Pain	2 (3.5%)	1 (1.9%)	0
Pruritis	2 (3.5%)	0	0
Constipation	1 (1.8%)	2 (3.7%)	1 (1.5%)
Paresthesia	1 (1.8%)	2 (3.7%)	0

(c) Serious clinical adverse experience were reported in 3 patients:

A 59 year old male with hypertension and atherosclerosis receiving famotidine 40 mg h.s. was admitted to the hospital on day 69 with a 2-week history of a severe right-sided head and face pain with 3 to 4 episodes of transient blindness in the right eye. A CT scan demonstrated a recent infarct in the distribution of the right middle cerebral artery. Angiography showed complete occlusion of the right, and partial occlusion of the left internal carotid. Therapy with famotidine was discontinued. The investigator considered this experience not drug-related.

A 50 year old male with a prior history of hemoptysis was receiving famotidine 40 mg h.s. when a diagnosis of pulmonary tuberculosis was made and the drug was discontinued on study day 36. The investigator believed the experience was definitely not related to drug therapy.

A 61 year old female with chronic obstructive pulmonary disease was admitted to the hospital with non-specific chest pains of 2 days duration after 42 days on placebo. The patient has been lost to follow-up. The investigator considered the experience definitely not drug-related.

(d) Laboratory adverse events were not serious and were no more frequent in the famotidine-treated patients than in the placebo-treated patients (table 23). There were 2 withdrawals from the trial in the famotidine group, one in the placebo group because of adverse laboratory events, but a drug-relationship was extremely doubtful in all cases.

TABLE 23

Laboratory Adverse Events/Number at Risk

	Famotidine 20 HS N=57	Famotidine 40 HS N=54	Placebo N=66
Hematology	3/52	5/54	1/64
Renal Function	0/51	3/53	0/64
Liver Function	11/51	3/53	13/64
Metabolic	3/51	0/54	0/60
Urogenital	3/51	6/54	9/60

(4) Effectiveness

(a) Incidence of recurrence: the sponsor's tabulation divides the duration of treatment into 3 periods, days 1-42, 43-105 and 106 or later (table 24). By life-table analysis it is clear that the incidence of recurrence with placebo (67%) is statistically significantly higher at the end of the 6 month trial than that with famotidine 40 mg h.s. (31%) and 20 mg h.s. (26%). However, because of the wide spread of the intervals allowed for the respective periods (e.g., period 3, the 6-month interval, includes endoscopies performed from day 106 onward) an endoscopic finding at 15 or 16 weeks would be included in the 24 week analysis. To get some conception of the rate as well as the incidence of recurrence, I requested the sponsor to prepare a tabulation showing the numbers for each 4-week period (table 25). From these data it is clear that, as has been shown in

TABLE 24

Cumulative Percent Recurrence, Life-Table Analysis

	40 HS	20 HS	PLACEBO	p
Period 1 (days 1-42)	0	1.8	12.1	40 HS <0.01; 20 <0.05 PLA
Period 2 (days 43-105)	15.2	17.8	51.4	40 HS <0.01; 20 <0.01 PLA
Period 3 (days 106 or later)	30.6	25.5	66.7	40 HS <0.01; 20 <0.01 PLA

TABLE 25

Number of Patients Who Relapsed (%)* (Life Table Rate)

	FAMOTIDINE 40 HS (N=56)	FAMOTIDINE 20 HS (N=57)	PLACEBO (N=66)
Month 1 (Days 1-28)	0 (0)	0 (0)	3 (5)
Month 2 (Days 29-56)	1 (2)	1 (2)	10 (18)
Month 3 (Days 57-84)	2 (4)	1 (2)	13 (22)
Month 4 (Days 85-112)	8 (19)	9 (18)	20 (54)
Month 5 (Days 113-140)	8 (19)	10 (21)	33 (62)
Month 6 (Days 141-168)	8 (19)	10 (21)	34 (64)
After Month 6 (Days 169-231)	11 (32)	12 (26)	35 (67)

*All Patients Treated Analysis

previous trials of prevention of recurrence, the recurrences tend to occur within the first 4 months. The bottom line, however, remains the same, in that the data provide evidence of effectiveness of famotidine in both dosages in reducing the incidence of recurrence of duodenal ulcer.

(b) Antacid consumption: the percent of patients taking antacids during the trial was the same on famotidine 40 h.s. (12%), 20 h.s. (14%) and placebo (15%).

e. Summary: 177 of the patients whose duodenal ulcers had healed in the short-term trial were admitted to a one year trial of famotidine, 40 mg h.s., 20 mg h.s. or placebo in the prevention of recurrence. At the time of this submission data were insufficient to report on the results beyond 6 months. The limited achievement of short-term healing is illustrated by the 67% incidence of recurrence in 6 months in patients receiving placebo. Both doses of famotidine reduced the incidence by about the same order of magnitude; the sponsor's recommended "maintenance" dose, 20 mg h.s., yielded a 26% incidence of recurrence. In this trial the drug was safe; clinical and laboratory adverse experiences were no more frequent in patients receiving the drug than in those receiving placebo.

f. Comment: bringing about healing of the duodenal ulcer in the short-term is no great clinical problem; it can be achieved as well with a few daily doses of antacid as with any of the systemically acting drugs. The problem in peptic ulcer disease is to prevent recurrence and thereby avoid intractability. Famotidine is clearly superior to placebo in this respect

but the 21% incidence of recurrence within 6 months with the recommended dose of 20 mg h.s. still leaves quite a bit to be desired. To compare the effectiveness of famotidine with that reported for other drugs it will be necessary to await the completion of the 1-year trial.

A single bedtime dose would have a cost-effective advantage, but as for the contention that it improves compliance, I doubt that patients would be any less compliant with a regimen of one tablet in the morning and one tablet in the evening. Since it may be possible to achieve even greater effectiveness in the prevention of recurrence than was obtained in this trial, the sponsor should consider a trial of a dose of 40 mg b.i.d., or perhaps 40 mg in the morning and 20 mg in the evening.

3. Study No. 41

a. Title: An open-label study to evaluate the use of famotidine in patients with peptic ulcer, Zollinger-Ellison Syndrome resistant to or intolerant of cimetidine or ranitidine or both.

b. Design of study: Open-label, uncontrolled study.

c. Investigator: Sidney Cohen, M.D., Hospital of the University of Pennsylvania, Philadelphia, PA.

d. Results (table 26)

(1) Characteristics of patients entered into the study: the basal acid output in the first 3 patients in the table is surprisingly low, especially in the face of the elevated serum gastrins.

(2) Safety: two of the patients had adverse effects, both requiring discontinuation from the study. One patient had severe abdominal pain, the other elevated liver enzymes which, however, were not clearly attributable to famotidine since the patient had had multiple blood transfusions and the enzymes were slightly elevated prior to entry into the study.

(3) Effectiveness: famotidine controlled the symptoms in all patients on doses titrated to the individual patient; doses as high as 400 mg/day were required. Three patients had been receiving famotidine for approximately one year at the time of this report (January 25, 1984).

e. Summary: a satisfactory response to therapy was achieved in 7 patients with possible or proven Z-E syndrome who had not been adequately controlled or had had adverse effects on cimetidine or ranitidine.

f. Conclusions: famotidine was usually well tolerated in patients with Z-E syndrome and may be useful in patients resistant to or intolerant of other H_2-blockers.

TABLE 26

Zollinger-Ellison Patients Treated With Famotidine

Patient No.	Age	Sex	BAO meq/hr	Maxm meq/hr	Gastrin pg/ml	Diagnosis	Concomitant Conditions	Previous Therapy	Reason Previous Therapy Discont.	Final Dosage mg	Duration in Study	Adverse Events
1	64	M	1.8	19.2	298	Probable Z-E	sick sinus syndrome, asthma	Cimetidine	Serum Creatinine Gynecomastia	60 BID	1 yr.	
2	44	M	10.2+		461	Z-E	MEA, hypothyroidism,	Cimetidine Ranitidine	Recurrent ulcer on cimetidine	100 AM 150 PM	1 yr.	
3	63	F	7.5	-	500	Z-E	None	Cimetidine Ranitidine	Decreased effectiveness on cimetidine Recurrent ulceration on ranitidine	20 BID	1 yr.	
4	33	M	75	90	1762	Z-E	Hypertension	Cimetidine Ranitidine	Severe abdominal pain	N/A	1 day	Severe abdominal pain discontinued from study
5	24	M	37.7	65.3	797	Z-E	None	Cimetidine Ranitidine	Recurrent pain and ulcer on cimetidine	80 BID	5 wks.	
6	47	M	4.5 (Tumor Metastatic)			Z-E	None	Cimetidine Ranitidine	CNS side effect Recurrent anastomatic ulcers on cimetidine	100 QID	2 wk.	Liver enzymes elevated, discontinued from study.
7	53	F	61.0		476	Z-E	COPD anxiety hives	Cimetidine Ranitidine	Decreased effectiveness on cimetidine	60 QID	1 mo.	

*BAO-Basal acid output per hour, **MAO Maximal acid out per hour, +Obtained in 1981

4. Study No. 6

a. Title of study: the use of famotidine in patients with hypersecretion of acid.

b. Investigator: Robert T. Jensen, M.D., Digestive Disease Branch, NIH, Bethesda, MD.

c. Design of study: open study divided into an acute phase and a long-term phase. The acute phase was conducted to compare the potency, onset of action, and duration of action of famotidine with cimetidine and ranitidine. A non-randomized block design was used.

Patients included in the study met the criteria of Zollinger-Ellison syndrome defined by a basal gastric acid output greater than 15 mEq/hr, a fasting serum gastrin concentration of greater than 100 pg/ml (normal less than 100 pg/ml), and a rise in the serum gastrin concentration of greater than 200 pg/ml after intravenous infusion of 2 units/kg of secretin. Patients under 18 years of age or women capable of becoming pregnant were excluded.

The critical evaluation criterion in this study was the level of hourly gastric acid output. An effective dose was defined as that which maintained the gastric acid secretion below 10 mEq/hour in the sixth hour following a dose.

At the start of the study, H_2-blockers were discontinued and gastric acid secretion was followed until it rose above 10mEq/hour. At that time, famotidine 20 to 60 mg was given every six hours for at least 4 doses. Selection of the starting dose of famotidine was based on the patient's response to previous treatment with H_2-blockers. Famotidine dosage was adjusted by 20 mg increments every 6 hours until the gastric acid output during the sixth hour post-drug was below 10 mEq. This dose was continued through the next day and gastric secretion measured again to ensure suppression of gastric acid to below 10mEq/hour.

The minimum 6-hourly doses of cimetidine and ranitidine were determined similarly; the adjustment increment of cimetidine was 300 mg, of ranitidine 150 mg, every 6 hours.

If doses of more than 160 mg of famotidine, 1500 mg of ranitidine, or 3,600 mg of cimetidine were required every 6 hours, the patient was defined as resistant to the respective drug and an anticholinergic, isopropamide 5 mg, was given every 6 hours in addition to the H_2-blocker. The minimum 6-hourly dose requirements were then determined as described above. The minimum doses of each drug that reduced gastric acid secretion to the same degree (to below 10 mEq/hr during the sixth hour after a dose) were considered equipotent.

In the long-term phase patients were treated continuously with famotidine alone for up to 38 weeks to investigate the safety, tolerability and required adjustments of the famotidine maintenance dose. They were evaluated at two weeks, two months and thereafter at two monthly intervals after beginning famotidine therapy. The initial dose was the minimum dose identified in the short-term study. Dosage was titrated as needed to ensure continued suppression of gastric acid below 10 mEq/hour.

d. Results

(1) Characteristics of patients studied (table 27): 11 patients were evaluated. It is obvious that they were all sick people.

TABLE 27

Characteristics of Patients Treated With Famotidine

Pt. No.	Age	Sex	Disease Duration (Yrs.)	Tumor Status	Prior Antisecretory Therapy	Basal Acid Output (mEq/hr)	Gastrin Basal (pg/ml)	Secondary Diagnoses
1	48	M	3	None	Ranitidine DANBID	55.6	184	Peripheral vascular disease, chest pain.
2	61	F	7	Suspected	Cimetidine	40.1	4,100	Liver mal., obesity, diabetes, low back pain.
3	55	M	1	None	Ranitidine	28.4	87-94	Myocardial infarction, borderline diabetes, chronic bronchitis.
4	54	M	7	Proven*	Ranitidine	44.6	15-30,000	Diabetes, Gilbert's Syndrome.
5	65	M	6	Suspected	Ranitidine	35.0	1,780	Cancer of prostate, hypertension.
6	22	M	2	Proven*	Ranitidine DANBID	44.4	520-590	Deep vein thrombosis.
7	48	F	5	None	Cimetidine DANBID	24.0	430	Obesity menorrhagia.
8	54	M	15	None	Cimetidine DANBID	108.3	3,045	Multiple sclerosis, Barrett's esophagus, colon polyps, alcohol liver disease.
9	47	F	2	Proven*	Cimetidine	18.1	7,000	Obesity, Hyperthyroidism, idiopathic cyclic edema.
10	55	M	7	Suspected	Ranitidine DANBID	50.0	2,200	Hyperthyroidism, L adrenal mass, prostatic hypertrophy
11	66	M	7	None*	Ranitidine	38.2	615	mild chronic renal failure, alcoholic induced fatty liver;
Mean						44.2	4,091	upper motor neuron disorder.

*Laparotomy performed, **Pancreatic tail lesion resected.

(a) Clinical adverse experiences: possibly drug-related symptoms prompted discontinuation of famotidine in 2 patients. Pre-existing alopecia in a woman worsened after 80 days; intermittent fever occurred in a male patient on famotidine for 252 days.

(b) Laboratory adverse events: famotidine was discontinued in 2 patients, one after 160 days with increased SGPT which was present at the outset and one after 241 days with marginal eosinophilia, elevated ESR and leukopenia.

(2) Effectiveness

(a) Relative potency of famotidine vs cimetidine and ranitidine: famotidine averaged 34 times as potent as cimetidine (range 15-75), 9 times as potent as ranitidine (range 2.5-15).

(b) Onset of action (figure 37): there was no difference among the 3 drugs in the rate of onset of action.

(c) Duration of action (figure 38): mean hourly gastric acid output remained below 10 mEq for 8 hours post-famotidine administration while the mean acid output at that interval was about 12 mEq with both cimetidine and ranitidine, not an impressive difference. From the 10th to 12th hours, however, acid was more effectively suppressed with famotidine than with either of the other drugs.

Figure 38
Duration of Action of Famotidine, Cimetidine, and Ranitidine

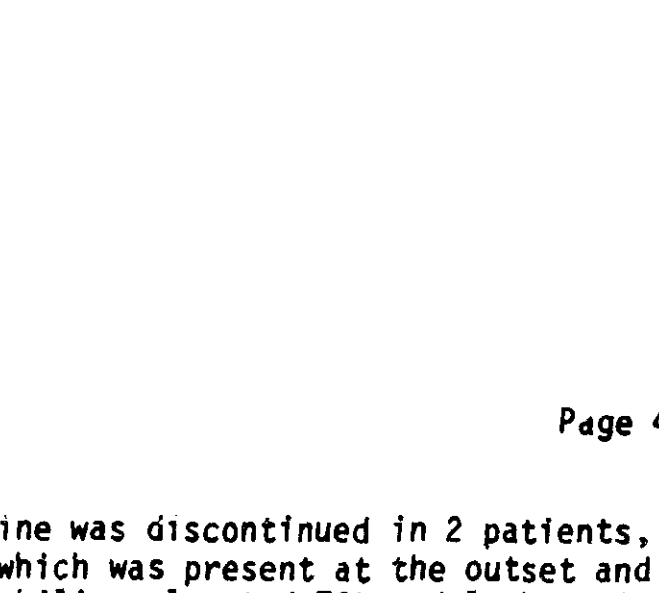
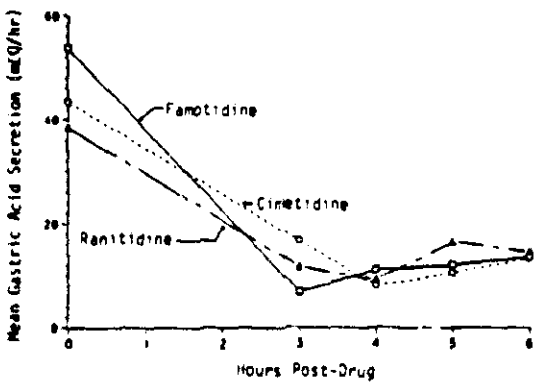


Figure 37
Onset of Action of Famotidine Compared With Cimetidine and Ranitidine (N = 4)



e. Summary: The summary and conclusions are set forth succinctly in the published paper by Howard et al (Gastroenterology 1985; 88:1026-1033, reprint attached). Famotidine was similar to the two other H_2-blockers in that equipotent doses had the same onset of action, time to maximum activity, patient tolerance, lack of evidence of hepatotoxicity and hematotoxicity, requirement for periodic adjustment of dose, and correlation among individual daily doses required to control gastric secretion. Famotidine differed from the other two drugs in that it had a longer duration of action, possibly attributable to a longer occupation of the H_2-receptor site,which, however, does not necessarily result in a less frequent dosing interval. Famotidine differed from cimetidine in that long-term high-dose treatment in males was not associated with anti-androgen side effects.

B. Foreign clinical trials

1. Study No. 5006

a. Title of study: 'A double-blind study in out patients to compare famotidine with ranitidine in the short-term treatment of duodenal ulceration.

b. Design of study: the protocol for this trial was identical to that outlined for the U.S. multicenter trial except that (1) instead of placebo, the reference control treatment was ranitidine 150 mg b.i.d, and (2) scores for severity of pain and of other symptoms were defined:

(1) Day pain

0 none
1 mild = bothered a little; pain is present part of the day, but causes little or no discomfort.
2 moderate = bothered to some degree; pain is present most of the day, annoying, but not interfering with daily routine.
3 severe = bothered intensely; constant pain causing marked interference with daily routine.

(2) Night pain

0 none
1 mild = bothered a little; pain is present part of the night, but does not interfere with sleep.
2 moderate = bothered to some degree; pain is present most of the night, occasionally interferes with sleep.
3 severe = bothered intensely; constant pain, marked interference with sleep.

(3) Other symptoms

(a) abdominal discomfort
(b) feeling of fullness
(c) flatulence
(d) acid regurgitation
(e) heartburn
(f) nausea
(g) vomiting
(h) other

(4) Severity of these symptoms was scored as follows:

0 none
1 mild = awareness of sign or symptom, but easily tolerated.
2 moderate = discomfort enough to cause interference with usual activity.
3 severe = incapacitating with inability to work or carry out usual activity.

(5) Global response to therapy was assessed by the patient as follows:

4 excellent = best possible anticipated response; abdominal pain completely relieved, other symptoms improved or no worse than usual.

3 good = good response; abdominal pain almost completely relieved, other symptoms improved or no worse than usual.

2 fair = definite response, but could be better; some relief of abdominal pain, other symptoms unchanged or worse.

1 poor = minimal response; little or no relief of abdominal pain, other symptoms unchanged or worse.

0 none = no response, absence of drug affect.

(5) The dosage schedule was as follows (all doses in milligrams):

Treatment Group	8:00 AM	10:00 PM
Famotidine 40 h.s.	placebo famotidine placebo ranitidine	famotidine 40 placebo ranitidine
Famotidine 20 b.i.d.	famotidine 20 placebo ranitidine	famotidine 20 placebo ranitidine
Famotidine 40 b.i.d.	famotidine 40 placebo ranitidine	famotidine 40 placebo ranitidine
Ranitidine 150 b.i.d.	placebo famotidine ranitidine 150	placebo famotidine ranitidine 150

c. Investigators (table 28): 68 investigators in 19 countries, all qualified by training and experience to conduct clinical trials, participated in this study.

d. Results

(1) Comparability of treatment groups (table 29): the number of patients in the respective groups were famotidine 40 h.s. 255, 20 b.i.d. 259, 40 b.i.d. 258, ranitidine 150 b.i.d. 259. The four treatment groups were essentially comparable in numbrs and in all other respects. There was no significant difference in the mean age between males and females.

TABLE 29

Comparability of Treatment Groups

	FAMOTIDINE 40 HS (n=255)	FAMOTIDINE 20 BID (n=259)	FAMOTIDINE 40 BID (n=258)	RANITIDINE 150 BID (n=259)
Age (Years), Mean	43.5	43.1	43.1	45.4
Sex				
Males	177 (69%)	173 (67%)	195 (76%)*	195 (75%)*
Females	78 (31%)	86 (33%)	63 (24%)	64 (25%)
Weight (kg)	68.5	69.6	69.8	69.3
Smoking	155 (61%)	150 (58%)	160 (62%)	146 (57%)
Alcohol	126 (50%)	121 (47%)	114 (44%)	121 (47%)
Initial Ulcer Size(cm)[a], Mean	0.96	0.91[e]	0.94[f]	0.91
Number of Ulcers				
One (90%)	225 (88%)	230 (89%)	230 (89%)	232[b]
Two or More	30 (12%)	29 (11%)	28 (11%)	26 (10%)
Age at First Ulcer(Years), Mean	38.4[c]	38.0	37.7	38.9[d]
Duration of Ulcer Disease (Years), Mean	5.1[c]	5.0	5.4	6.6[d]
Ulcer History				
None	75 (29%)	77 (30%)	79 (31%)	71 (27%)
One Previous Episode	75 (20%)	65 (25%)	67 (26%)	62 (24%)
Multiple Previous Episode	105 (42%)	117 (45%)	112 (43%)	126 (49%)
Other Pathology in Esophagus	25 (10%)	32 (12%)	32 (12%)	31 (12%)
Other Pathology in Stomach	51 (20%)	50 (19%)	54 (21%)	64 (25%)
Other Pathology in Duodenum	113 (44%)	108 (42%)	121 (47%)	117 (45%)
Concomitant Conditions				
Anemia	6 (2.4%)	1 (0.4%)	0	0
Anxiety disorders	2 (0.8%)	4 (1.5%)	4 (1.6%)	8 (3.1%)
Asthma	1 (0.4%)	1 (0.4%)	6 (2.3%)	4 (1.5%)
Cholecystectomy	5 (2.0%)	10 (3.9%)	7 (2.7%)	4 (1.5%)
Hypertension	13 (5.1%)	16 (6.2%)	10 (3.9%)	14 (5.4%)
Insomnia	5 (2.0%)	3 (1.2%)	0	1 (0.4%)

*Significantly different from the famotidine 20 BID group (p<0.05).
[a]For patients with more than one ulcer, this was the size of the largest ulcer.
[b]One patient did not have a duodenal ulcer.
[c]n=254, [d]n=257, [e]n=258

Table 28

Argentina		
De Paula, A.O.F.	Director of the Hospital	Ramos Mejia Hospital, Buenos Aires
Kohan, S.	Chief of Gastroenterology	Pirovano Hospital, Buenos Aires
Segal, J.E.	Chief of Gastroenterology	Durand Hospital, Buenos Aires
Australia		
Goulston, K.J.	Specialist in Gastroenterology	Concord General Hospital, Sydney
Mansky, J.	Gastroenterologist	Prince Henry's Hospital, Melbourne
Piper, D.W.	Visiting Medical Officer	Royal North Shore Hospital, St. Leonards
Shearman, J.C.	Chairman, Dpet. of Medicine	Royal Adelaide Hospital, Adelaide
Austria		
Mentschel, E.	Internist	Hanusch Hospital, Vienna
Reichel, W.	Director of Endoscopical	Wilhelminen Hospital, Vienna
Schitze, K.	Specialist in Internal Medicine	Hanusch Hospital, Vienna
Brazil		
Bettarello, A.	Professor	Medical School of Sao Paulo
Castro L.	Gastroenterologist	Federal University of Minas Gerais, Belo Horizonte
Canada		
Archambault, A.	Head of Gastroenterology	Maisonneuve-Rosemont Hosp.,Montreal
Hunt, R. H.	Head of Gastroenterology	McMaster U. Med. Cent. Hamilton
Mercon, N.E.	Head of Gastroenterology	The Wellesley Hospital, Toronto
Colombia		
Aponte, L.	Endoscopist/Gastroenterologist	Carrera 18 No. 80-67, Bogota
Denmark		
Rokkjaer, M.	Head Surgeon	Arhus Council Hospital, Arhus
England		
Brown, P.	Consultant Physician	Royal Shrewsbury Hosp., Shrewsbury
Cockel, R.	Consultant Physician	Selly Oak Hospital, Birmingham
Cowan, R.E.	Consultant Physician	Essex County Hospital, Colchester
Fairclough, P.D.	Consultant Physician	St. Bartholomew's Hospital, London
Garnham, J.C.	Endoscopiest	Wexham Park Hospital, Slough
Levi, A.J.	Consultant Gastroenterologist	Northwick Park Hospital, Harrow
Record, C.O.	Consultant Physician	Royal Victoria Infirmary,Newcastle
Vicery, F.R.	Consultant Physician	Whittington Hospital,London
Finland		
Reyrilainen, O.	Chief of Gastroenterology	University Central Hosp.Tampere
Salaspuro, M.P.J.	Chief, Gastroenterology	University Central Hosp.Helsinki
France		
Carayon, P.	Head of Gastroenterology	Centre Hosp. Regional,Besancon
Chaput, J.	Head of Gastroenterology	Hospital Antoine Beclere,Clamart
Ferrier, J.P.	Dept. Head, Gastroenterology	Hospital Jean Verdier,Bondy
Paris, J.C.	Dept. Head, Gastroenterology	Centre Hospitalier Regional,Lille
Ribet, A.	Dept. Head, Gastroenterology	U. Hospital of Toulouse-Ranguell
Germany		
Dammann, H.G.	Gastroenterologist	Bethanien Hospital, Hamburg
Jakob, G.	Head, Dept. Gastroenterology	District Hosp.Eichstaett, Eichstaett
Miederer, S.E.	Professor of Gastroenterology	Medical University Poliklinik, Bonn
Ottenjann, R.	Head of Internal Medicine	Municiple Hosp.Mue Neuperlach, Munich
Paul, F.	Head of Medical Clinic II	Klinik Ingolstadt, Ingolstadt/Donau
Scholten, T.	Assistant Professor Gastro-enterology	Med. Klinik u. Poliklinik
Schuetz, E.	Internist/Gastroenterologist	University Duesseldorf
Seifert, E.	Head of Gastroenterology	Gastroenterology-Proktology, Regensburg
Simon, B.	Specialist for Gastroenterology	Municipal Hospital Kemperhof, Koblenz
Stadelmann, O.	Head of Dept. of Gastro-	Medical University Klinik, Heidelburg
		ChA d. Medical Klinik II, Fuerth
Holland		
Kettner, M.	Internist	Gasthuis Middelburg, Middelburg
Mesdorp, I.C.E.	Gastroenterologist	Andreas Hospital, Amsterdam
Ireland		
Crowe, J.	Gastroenterologist	Mater Misericordiae Hospital, Dublin
Gleeson, F.	Consultant Physician,Lecturer	James Connolly Memorial Hosp., Dublin
Weir, D.G.	Consultant Gastroenterologist	St. James' Hospital, Dublin
Italy		
Bagliont, A.	Surgeon, Lecturer	Hospital Generale Provinciale
Barbara, L.	Director of Gastroenterology	Hospital Sant'Orsola, Bologna
Bianchi-Porro,G	Director of Gastroenterology	Hospital L Sacco, Milan
Blasi, A.	Director of Gastroenterology	Hospital Vittorio Emanuele II, Catania
Carotenuto, F.	Head Surgeon	Municipal Hospital of Cassino,
Chell, R.	Chief Dept. of Gastroenterology	Hospital S. Martino, Genova
Dal Monte, P.R.	Head Gastroenterologist	Hospital Bellaria, Bologna
Francavilla, A.	Head Physician	Cattedra di Malattie Apparato Digerent, Bari
Materazzo, P.F.	Assistant Surgeon	Municipal Hospital of Formia,
Mazzacca, G.	Div. of Gastroenterology	
Paoluzi, P.	Gastroenterologist	School of Medicine, Naples
Speranza, V.	Head of Surgical Clinic	II Clinical Medica Universita di Roma
		VI Clinical Chirurgica
Toti, F.	Head Surgeon	University degli Studi di Roma
Vagni, V.	Consultant Endoscopist	Municipal Hospital of Subfaco
Verme, G.	Head Physician	Municipal Hospital,Castellana
		Hospital Molinette, Torino
Mexico		
VillaTobos, J.	Head of Dept. of Gastroenterogy	National Institute of Nutrition, Mexico,D.F.
New Zealand		
Tasman-Jones,C.	Associate Professor	Auckland Med.School,Auckland
Norway		
Fause, O.	Head of Dept. of Gastro-enterology	Riks Hospital, Oslo
South Africa		
Dantzwitz, M.D.	Head, Medical Gastroenterology	Johannesburg Hosp.,Parktown
Marks, I.N.	Head, Gastrointestinal Clinic	Groote Schuur Hospital,
Sweden		
Mradsky, M.	Chief of Gastroenterology Unit	Falu Hospital, Falun

(2) Exclusions from analysis of effectiveness: the number of patients excluded from analysis of healing because of protocol violations (table 30) was gratifyingly small, amounting to a total of 5%. Even the numbers lost from analysis because of absence of data on pain and global response (table 31) left a sufficiently large data base for meaningful analysis.

TABLE 30

Exclusions from Analysis of Effectiveness

Protocol Violation	Famotidine 40 HS	Famotidine 20 BID	Famotidine 40 BID	Ranitidine 150 BID	Total
Concomitant Drug	7	2	5	5	19
Initial Endoscopy or Ulcer Size Out of Range	5	6	3	4	18
Prior Surgery	1	0	1	0	2
Uncooperative Patient	2	4	2	4	12
TOTAL	15	12	11	13	51

TABLE 31

Number of Patients Omitted From Analysis of Effectiveness

	Famotidine 40 HS N=255			Famotidine 20 BID N=259			Famotidine 40 BID N=258			Ranitidine 150 BID N=259		
	WK 2	WK 4	WK 8	WK 2	WK 4	WK 8	WK 2	WK 4	WK 8	WK 2	WK 4	WK 8
Protocol Violators	15	15	15	12	12	12	11	11	11	13	13	13
No Day/Night Pain Data	25	21	20	20	17	20	18	17	18	21	19	19
No Global Response Data	44	23	23	37	16	17	39	18	18	40	18	18
NUMBER EVALUABLE												
Ulcer Healing	240	240	240	247	247	247	247	247	247	246	246	246
Day/Night Pain	230	234	235	239	242	239	240	241	240	238	240	240
Global Response	211	232	232	222	243	242	219	240	240	219	241	241

(3) Safety

(a) Vital signs (table 32): changes during treatment from baseline value were statistically significant for some or all of the treatments, but none of the changes were of clinical concerr.

TABLE 32

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE	COMMENTS
Weight (kg)	40 HS	244	68.8	68.8	0.3	Increase for each treatment (p 0.01)
	20 BID	252	69.6	69.0	0.2	
	40 BID	247	69.8	70.0	0.2	
	Ranit	249	69.3	69.7	0.4	
Pulse	40 HS	239	75.9	74.0	-1.0	40 BID lower than 40 HS and 20 BID (p 0.5)
	20 BID	248	75.2	74.6	-0.6	
	40 BID	240	73.6	73.4	-0.2	
	Ranit	242	74.4	74.0	-0.4	
Systolic BP (mmHg)	40 HS	238	126.0	124.7	-1.3	No significant dofferences
	20 BID	249	126.9	126.5	-0.4	
	40 BID	241	126.1	125.6	-0.5	
	Ranit	244	129.9	128.7	-1.2	
Diastolic BP (mmHg)	40 HS	238	79.6	78.5	-1.1	40 HS and 40 BID decreased p 0.05
	20 BID	249	79.6	79.1	-0.5	
	40 BID	241	79.6	78.6	-1.0	
	Ranit	243	79.3	78.7	-0.6	

(b) Clinical adverse events: adverse symptoms occurring with an incidence of 1.5% or more in at least one of the treatment groups (table 33) were primarily in the central nervous system (CNS) (famotidine 6%, ranitidine 8%) and the gastrointestinal (GI) system (famotidine 4%, ranitidine 5%). The most common CNS symptom, headache, occurred in 4% on both famotidine and ranitidine. The incidence of the most common GI symptom, diarrhea, was 1.3% on famotidine, 1.9% on ranitidine. The adverse experiences were considered serious in only 2/772 (0.2%) of patients receiving famotidine, 3/259 (1.2%) of those receiving ranitidine. Very few of the adverse symptoms were drug-related; e.g. the incidence of withdrawal of patients because of adverse experiences (table 34) was very low. Moreover such events as hemorrhage, development of a gastric ulcer or perforation of a duodenal ulcer are more appropriately classified as failures of therapy than as adverse drug effects.

TABLE 33

Clinical Adverse Experiences by Body System (%)

	Famotidine 40 HS (N=255)	Famotidine 20 BID (N=256)	Famotidine 40 BID (N=258)	Ranitidine 150 BID (N=259)
Body as a whole	5 (2.0)	7 (2.7)	4 (1.6)	5 (1.9)
Cardiovascular	3 (1.2)	0	1 (0.4)	0
Digestive	10 (3.9)	12 (4.6)	11 (4.3)	12 (4.6)
Hemic/Lymphatic	0	0	0	1 (0.4)
Metabolism	1 (0.4)	0	0	0
Musculoskeletal	2 (0.8)	3 (1.2)	2 (0.8)	0
Nervous/Psychiatric	13 (5.1)	13 (5.0)	20 (7.8)	20 (7.7)
Respiratory	3 (1.2)	5 (1.9)	8 (3.1)	3 (1.2)
Tegumentary	4 (1.6)	4 (1.5)	1 (0.4)	5 (1.9)
Special Senses	0	0	0	1 (0.4)
Urogenital	0	1 (0.4)	0	0
Total	41 (16)	45 (17)	47 (18)	47 (18)

TABLE 34

Patients Withdrawn Due To Adverse Experience

TREATMENT GROUP	AN	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	TOTAL POSSIBLY/ PROBABLY
Famotidine 40 HS	172	Abdominal pain	Severe	Probably not[a]	
		Eructation	Severe	Probably not	
	42	Diarrhea	Severe	Possibly	
	542	Headache	Severe	Possibly	
	590	G.I. bleeding	Severe	Definitely not	
	1055	Gastric ulcer	Mild	Probably not	4/255 (1.6%)
Famotidine 20 BID	759	Gastric ulcer	Mild	Probably not	
	1130	Perforated duodenal ulcer	Moderate	Probably not	2/259 (0.7%)
Famotidine 40 BID	368	Pain, generalized	Severe	Possibly	
	465	Anorexia	Severe	Definitely	
		Anxiety	Severe	Definitely	
		Headache	Severe	Definitely	2/258 (0.8%)
Ranitidine 150 BID	52	Lung cancer	Severe	Definitely not	
	147	Diarrhea	Severe	Probably	
	721	Depression	Moderate	Possibly	
		Agitation	Moderate	Possibly	
		Concentration loss	Moderate	Possibly	
		Malaise	Moderate	Possibly	3/259 (1.2%)

[a] "Probably not" = "Possibly yes"

(c) Laboratory adverse events were infrequent (table 35), occurring in approximately 4% of patients in each group. No patient was withdrawn because of an abnormal laboratory finding.

TABLE 35

Laboratory adverse events/number at risk

	Famotidine 40 HS (N=255)	Famotidine 20 BID (N=259)	Famotidine 40 BID (N=258)	Ranitidine 150 BID (N=259)
Hematology	6/235	5/242	6/231	3/236
Liver Function	2/229	3/230	3/230	9/234
Renal Function	0/143	0/150	1/140	1/143
Metabolic	0/100	0/104	1/95	0/99
Urogenital	1/235	0/242	2/231	1/236

(4) Effectiveness

(a) Incidence of healing: the sponsor displays the data for incidence of healing at 2, 4, and 8 weeks in the conventional manner (table 36) in which the 2-week endoscopy could be as late as 18 days, the 4-week endoscopy as late as 34 days, and the 8-week endoscopy as late 64 days. The resulting numbers do not correctly reflect the interval of healing, as illustrated by the tabulation in which the incidence of healing is displayed by actual weeks (table 37). As in the U.S. trial, it is clear that the optimal interval to endoscope patients on treatment is 5 weeks. By both methods of calculation, the 20 mg b.i.d. and 40 mg b.i.d. doses of famotidine are more effective at 2, 4 and 8 weeks than the sponsor's proposed dose of 40 mg h.s.

TABLE 36

Cumulative Number Healed/Number Evaluable (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=240	Famotidine 20 BID N=247	Famotidine 40 BID N=247	Ranitidine 150 BID N=246
2 (Days 1-18)	82 (34)	94 (38)	109 (44)	96 (39)
4 (Days 19-34)	164 (68)	191 (77)*	201 (81)*	186 (76)
8 (Days 35-64)	210 (88)	228 (92)	227 (92)	222 (90)
Beyond week 8 (Days 65-72)	211 (88)	231 (94)*	231 (94)*	223 (91)

* Significantly higher than famotidine 40 h.s., p<.05.

TABLE 37

Cumulative Number Healed (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=240	Famotidine 20 BID N=247	Famotidine 40 BID N=247	Ranitidine 150 BID N=246
Week 1 (Days 2-8)*	0 (0)	0 (0)	0 (0)	0 (0)
Week 2 (Days 9-15)	62 (26)	72 (29)	84 (34)	72 (29)
Week 3 (Days 16-22)	87 (36)	99 (40)	114 (46)	100 (41)
Week 4 (Days 23-29)	141 (59)	165 (67)	173 (70)	163 (66)
Week 5 (Days 30-36)	169 (70)	194 (79)	203 (82)	191 (78)
Week 6 (Days 37-43)	170 (71)	197 (80)	206 (83)	192 (78)
Week 7 (Days 44-50)	170 (71)	197 (80)	206 (83)	193 (78)
Week 8 (Days 51-57)	186 (78)	211 (85)	219 (89)	207 (84)

* Day 1 was the day of the baseline evaluation. Patients started taking drug at bedtime on day 1. All week/day ranges start with day 2.

(b) The incidence of healing as reported by those investigators who had at least 20 patients (table 38) shows comparatively little treatment by investigator interaction at the important intervals (weeks 4 and 8) except for those intervals where the investigators had too few patients to make the differences meaningful. It is curious but inexplicible that in the sponsor's proposed dose (40 mg h.s.) for the short-term treatment, the total incidence of healing reported by the investigators with 20 or more patients was much higher (85%) than that of all of the rest of the investigators combined (63%). By whatever method the data are calculated, at week 2 and more importantly at week 4, the incidence of healing is higher with ranitidine b.i.d. than with the sponsor's recommended dose of famotidine 40 mg h.s.

TABLE 38

Incidence of Healing Reported by Investigators with at Least 20 Patients

Number (%) Healed

Investigator	City	Famotidine N	Famotidine 40 HS Wk 2	Famotidine 40 HS Wk 4	Famotidine 40 HS Wk 8	Famotidine 20 BID N	Famotidine 20 BID Wk 2	Famotidine 20 BID Wk 4	Famotidine 20 BID Wk 8	Famotidine 40 BID N	Famotidine 40 BID Wk 2	Famotidine 40 BID Wk 4	Famotidine 40 BID Wk 8	Ranitidine 150 BID N	Ranitidine 150 BID Wk 2	Ranitidine 150 BID Wk 4	Ranitidine 150 BID Wk 8
Archambault	Montreal	6	2 (33)	6 (100)	6 (100)	6	3 (50)	6 (100)	6 (100)	6	1 (17)	6 (100)	6 (100)	6	0 (0)	2 (33)	4 (67)
Dammann	Hamburg	12	7 (58)	11 (92)	11 (92)	9	6 (67)	8 (89)	8 (89)	11	9 (82)	11 (100)	11 (100)	8	4 (50)	7 (88)	7 (88)
Paul	Ingolstadt	12	7 (58)	10 (83)	10 (83)	12	7 (58)	9 (75)	11 (92)	12	8 (67)	9 (75)	10 (83)	11	6 (55)	10 (91)	10 (91)
Stiehm	Heidelberg	13	8 (62)	9 (69)	13 (100)	13	9 (69)	11 (85)	12 (92)	13	7 (54)	11 (85)	13 (100)	13	4 (69)	12 (92)	12 (92)
Crome	Dublin	7	4 (57)	6 (86)	7 (100)	8	3 (33)	6 (67)	8 (89)	8	5 (63)	6 (75)	7 (88)	9	2 (22)	6 (66)	7 (78)
Blanchet Pong	Milan	9	2 (22)	9 (99)	9 (100)	9	2 (22)	6 (67)	9 (100)	9	6 (68)	9 (100)	9 (100)	9	5 (56)	8 (89)	9 (100)
SUBTOTAL	--	59	30 (51)	50 (85)	56 (95)	58	30 (52)	36 (-0)	54 (93)	59	34 (58)	52 (88)	56 (95)	56	26 (46)	43 (77)	46 (82)
*Pool	--	181	52 (29)	114 (63)	154 (85)	180	64 (36)	1-9 (72)	176 (97)	188	75 (40)	140 (74)	171 (91)	190	70 (37)	143 (75)	173 (91)
TOTAL	--	240	82 (34)	164 (68)	210 (88)	247	94 (38)	91 (77)	229 (92)	247	109 (44)	201 (81)	227 (92)	246	96 (39)	186 (76)	222 (90)

*All Other Investigators Combined.

(c) Relief of pain: the percentage of patients relieved of day pain (figure 39) and night pain (figure 40) was the same at all recorded intervals for all 4 treatments. Contrary to what one might expect, time to relief of day pain (table 39) was no shorter in patients whose pain was mild on entry than in those with moderate to severe pain on entry, except for patients receiving ranitidine in whom the more severe the pain, the longer the time to relief. Time to relief of night pain was, however, more rapid with all treatments in patients with initially mild pain than in those with moderate or severe pain.

Figure 39

PERCENTAGE OF PATIENTS WITH NO DAY PAIN

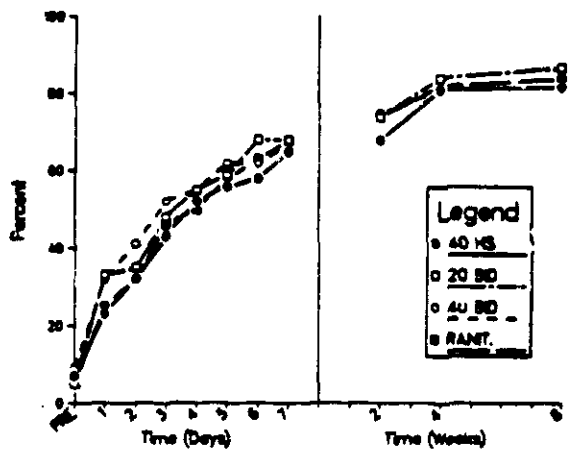


Figure 40

PERCENTAGE OF PATIENTS WITH NO NIGHT PAIN

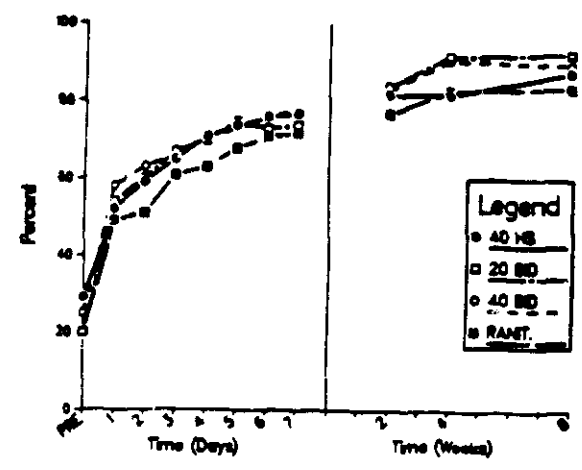


TABLE 39

Incidence n/, and Median, Time to Relief of Pain (Days)

		FAMOTIDINE 40 HS (n = 240)	FAMOTIDINE 20 BID (n = 247)	FAMOTIDINE 40 BID (n = 247)	RANITIDINE 150 BID (n = 246)
Day Pain					
Incidence (%)		224 (93)	235 (95)	224 (91)	234 (95)
Baseline *	None	1.0 (n = 16)	1.0 (n = 12)	1.0 (n = 23)	2.5 (n = 12)
	Mild	11.0 (n = 56)	8.0 (n = 48)	5.0 (n = 51)	4.5 (n = 62)
	Moderate	7.0 (n = 119)	6.0 (n = 112)	7.0 (n = 108)	7.0 (n = 100)
	Severe	7.0 (n = 51)	7.0 (n = 75)	7.0 (n = 65)	10.0 (n = 72)
	Total	7.0 (n = 240)	6.0 (n = 247)	6.0 (n = 247)#	7.0 (n = 246)
Night Pain					
Incidence (%)		171 (71)	197 (80)	186 (75)	197 (80)
Baseline *	None	1.0 (n = 69)	1.0 (n = 50)	1.0 (n = 62)	1.0 (n = 49)
	Mild	3.0 (n = 37)	3.0 (n = 50)	3.0 (n = 51)	3.0 (n = 57)
	Moderate	5.0 (n = 80)	5.5 (n = 86)	6.0 (n = 69)	14.0 (n = 65)
	Severe	7.0 (n = 54)	4.0 (n = 60)	7.0 (n = 65)	6.0 (n = 80)
	Total	3.5 (n = 240)	3.0 (n = 247)**	3.0 (n = 247)**	5.0 (n = 246)

* Some patients had no pain at baseline but had pain at one or more subsequent timepoints.
** Significantly shorter than the ranitidine group ($p < .01$)
\# Significantly shorter than the famotidine 40 HS group ($p < .05$)

(d) Antacid consumption: the percentage of patients receiving antacid therapy was consistently greater with ranitidine than with famotidine during the first 4 weeks, after which very few patients were still taking antacids (figure 41). During the first 2 weeks the mean number of days in which antacid therapy was taken was significantly greater with the patients receiving ranitidine than with those receiving the 2 b.i.d. doses of famotidine but the differences amount to only a fraction of a day (table 40). No difference emerged between ranitidine and the 40 h.s. dose of famotidine.

Figure 41
Percentage of Patients Receiving Antacid Therapy

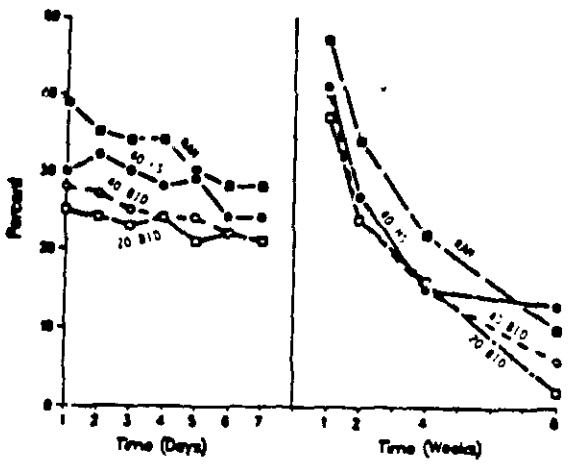


TABLE 40

Mean Days of Antacid Therapy, Mean ± Standard Deviation

WEEK	FAMOTIDINE 40 HS N	FAMOTIDINE 40 HS MEAN	FAMOTIDINE 20 BID N	FAMOTIDINE 20 BID MEAN	FAMOTIDINE 40 BID N	FAMOTIDINE 40 BID MEAN	RANITIDINE 150 BID N	RANITIDINE 150 BID MEAN	NUMBER OF DAYS DIFFERENCE BETWEEN 40 BID & RANITID
1	241	2.0 ± 2.7	250	1.6 ± 2.5**	249	1.7 ± 2.6*	247	2.3 ± 3.0	- 0.3
2	227	1.3 ± 2.4	239	0.9 ± 2.1**	237	1.1 ± 2.3*	237	1.6 ± 2.7	- 0.3
4	132	0.8 ± 2.0	140	1.0 ± 2.3	113	0.7 ± 1.9	129	1.2 ± 2.5	- 0.4
8	53	0.7 ± 1.9	41	0.28 ± 1.1	36	0.5 ± 1.8	40	0.7 ± 2.1	- 0.0

*,** Significantly different from the ranitidine group (p .05, p .01, respectively).
Significantly different from the 40 HS group (p .05).
Mean number of days of antacid therapy is the 7-day period ending the relative day of the pain measurements taken at this week. Since some patients have no pain measurements, numbers may differ.
N Number of patients evaluated.

e. Summary: 1,031 patients were entered into a multicenter trial of 3 doses of famotidine (40 mg h.s., 20 mg b.i.d. and 40 mg b.i.d.) vs ranitidine 150 mg b.i.d. in the short-term treatment of duodenal ulcer. The incidence of healing was:

WK	Fam 40 HS	Fam 20 BID	Fam 40 BID	Ran 50 BID
4	68%	77%	81%	76%
8	87%	92%	92%	90%

Thus the incidence of healing with ranitidine at the important 4 week follow-up was of the same order as that with famotidine 20 mg b.i.d. and 40 mg b.i.d. but was higher than with the sponsor's recommended dose of 40 mg h.s. The percentage of patients relieved of both day and night pain was in the neighborhood of 60% at the end of the first week and 80% at the end of 8 weeks with all 4 treatments. The time to relief of day pain in famotidine-treated patients was generally not shorter when the pain was initially mild than when it was moderate or severe, averaging 6-7 days. In patients receiving ranitidine the average time to relief of severe pain was 18 days contrasted with 4.5 days for mild pain. The average number of days in which patients took antacids differed by a fraction of a day among the 4 treatment groups, a clinically meaningless difference. The percentage of patients receiving antacids during the first 2 weeks of treatment was significantly less in patients receiving famotidine 20 mg b.i.d. than in those receiving ranitidine, but at no time point was there an advantage of the sponsor's recommended dose (40 mg h.s.) over ranitidine in the number of patients requiring concomitant antacid therapy. The incidence of drug-related adverse events requiring withdrawal of patients from famotidine treatment was less than 1%.

An interesting difference between the conduct of the U.S. and foreign trials in the short-term treatment of duodenal ulcer is that twice as many U.S. investigators contributed 10 or fewer patients, while twice as many foreign investigators contributed 11 or more patients. It would be instructive to know whether this difference is because the foreign investigators had more time to complete the assigned number of patients, had more patients available to them, are more persuasive in convincing patients to enter clinical trials, or whether patients are more easily persuaded to participate when the control substance is a drug of known effectiveness rather than a placebo.

2. Protocol No. 503-00

a. Title of study: A double-blind study in out-patients to compare famotidine with placebo in the long-term maintenance treatment of duodenal ulcer (weeks 1-24).

b. Design of study: the procedure was identical with that of the U.S. multi-center trial of prevention of recurrence except that only 1 dose of famotidine, 20 mg h.s., was compared with placebo.

c. Investigators: 64 of the 68 investigators listed in the short-term trial participated.

d. Results

(1) Comparability of patient groups (table 41): there were 306 patients on famotidine, 339 on placebo. The groups were comparable in all relevant respects.

TABLE 41

Comparability of Treatment Groups

	FAMOTIDINE 20 MG (N=306[a])	PLACEBO (N=339[a])
Age (Years), Mean	43.5	43.9
Sex		
Males	222 (73%)	237 (69%)
Females	84 (27%)	102 (30%)
Treatment in the Acute Study		
Famotidine 40 MG	76 (25%)	77 (23%)
Famotidine 20 BID	67 (22%)	100 (30%)
Famotidine 40 BID	82 (26%)	85 (25%)
Ranitidine Base 150 BID	79 (26%)	75 (22%)
Week Ulcer Healed in the Acute Study		
Week 2	133 (44%)	129 (38%)
Week 4	126 (42%)	141 (42%)
Week 8 or later	43 (14%)	67 (20%)
Smoking[b]	168 (55%)	208 (62%)
Drinking[b]	126 (41%)	166 (49%)
Initial Ulcer Size[b] (cm), Mean	0.91	0.90
Number of Ulcers[b]		
One	276 (91%)	304 (90%)
Two or More	28 (9%)	33 (10%)
Age at First Ulcer[b] (Years)		
Mean	38.2	38.2
Median	35.0	38.0
Duration of Ulcer Disease[b] (Years)		
Mean	5.6	5.7
Median	3.0	3.0
Ulcer History[b]		
None	82 (27%)	98 (29%)
One Previous Episode	83 (27%)	88 (26%)
Multiple Previous Episodes	139 (46%)	151 (45%)
Race		
Caucasian	270 (88%)	311 (92%)
Black	8 (3%)	7 (2%)
Hispanic	5 (2%)	7 (2%)
Other	22 (7%)	14 (4%)
Other Pathology in the Esophagus	19 (6%)	23 (7%)
Other Pathology in the Stomach	30 (10%)	31 (9%)
Other Pathology in the Duodenum	160 (54%)	191 (57%)

[a] Maximum counts, some patients had no information for some variables
[b] Status at the beginning of the short term study.

(2) Exclusions from analysis of effectiveness (table 42): 38/306 (12%) of patients receiving famotidine and 33/309 (10%) of patients receiving placebo were excluded, primarily because of various protocol violations, the most common of which were (a) failure to take the drug as prescribed and (b) taking forbidden concomitant medications. The percentage lost was in the same range as that in the U.S. trial.

TABLE 42

Exclusions from Analysis of Effectiveness

	Number of Patients (%) FAMOTIDINE N=306	PLACEBO N=339
Off Drug	16	10
Concomitant Medication	5	8
No Final Endoscopy	4	1
Patient Unreliable	4	3
Other Protocol Violations	7	5
Total	38(12)	33(10)

(3) Safety

(a) Vital signs: other than an increase in body weight, of no clinical import, in patients receiving famotidine compared with patients receiving placebo, there was no difference between the treatments with regard to change from baseline or difference from each other.

(b) Clinical adverse experiences (table 43) occurred with somewhat higher frequency in patients on famotidine (25%) than on placebo (19%); the difference is not statistically significant. Headache, the most common CNS symptom, occurred with equal frequency in the 2 groups (famotidine 2.6%, placebo 2.9%).

TABLE 43

Number of Patients with Adverse Experiences (%)

BODY SYSTEM	Famotidine 20 MS N = 306	Placebo N = 339
Central Nervous	16 (5.2)	20 (5.9)
Cardiovascular	3 (1.0)	1 (0.3)
Digestive	14 (4.6)	21 (6.2)
Respiratory	21 (6.9)	8 (2.4)
Tegumentary	7 (2.3)	6 (1.8)
Musculoskeletal	6 (2.0)	2 (0.6)
Hemic/Lymphatic	1 (0.3)	0
Special Senses	4 (1.3)	4 (1.2)
Urogenital	4 (1.3)	2 (0.6)
TOTAL	76 (25)	64 (19)

Symptoms evaluated by the investigator as possibly, probably or definitely drug-related were recorded in 5/306 (1.6%) of patients receiving famotidine, 9/339 (2.7%) of patients receiving placebo. The only really troublesome adverse clinical event in patients receiving famotidine was alopecia in one patient; however, it was also reported in one patient receiving placebo. Among patients 65 years of age or older clinical adverse experiences occurred in 8/18 (44%) on famotidine, 5/17 (29%) on placebo; however, the adverse experiences reported in this age group appeared to be related not to a drug-effect but rather to diseases associated with advancing age such as myocardial infarction, traumatic arthropathy, insomnia, Parkinson's disease and neoplasia. This is a reflection of the FDA requirement that all adverse events occurring during a clinical trial be reported; for example injury or death from a gunshot wound or a traffic accident while a patient is in a clinical trial must be reported as an adverse event which it obviously is, but which equally obviously has nothing to do with the treatment. Since such events could occur with equal frequency in patients receiving a drug as in those receiving a placebo, it is not surprising that, in a clinical trial of a drug as safe as famotidine, the percent of patients withdrawn because of adverse experiences in this trial was the same with famotidine, 9/306 as with placebo, 8/339 (2.4%). Interpretation of these numbers is complicated by the fact that investigators differ in their assessments of possibly/probably drug-related effects. These differences are illustrated in the 8 patients in whom serious adverse events were reported:

A 50 year old man receiving famotidine experienced 2 episodes of hematemesis and hematochezia on day 34. Endoscopy 2 days later revealed a 2.0 cm duodenal ulcer with signs of bleeding. Following gastric resection the patient had an uneventful recovery. The investigator assessed this occurrence as probably not drug-related.

The duodenal ulcer in a 50 year old man with tarry stools on entry into the short-term trial healed complete on ranitidine; the patient was enrolled in the maintenance study on famotidine. On day 85 endoscopy revealed hemorrhagic gastritis. On day 123 the patient reported fulness; endoscopy showed bleeding varices in the gastric fundus. Carcinoma of the pancreas was suspected and was confirmed at surgery on the following day. The investigator's opinion was that this was probably not a drug-related event.

A 70 year old man was hospitalized because of chest pain on day 8 of treatment with famotidine. There were no significant changes in the ECG; enzyme levels were not raised. After discharge, medication was restarted. On day 77 the patient again experienced chest pain and was withdrawn from the study. He later underwent surgery for pneumothorax. The investigator thought that this occurrence was probably not drug related.

A 48 year old man experienced asthenia, headache and dizziness during treatment with ranitidine in the short-term study. In the maintenance study he was randomized to receive famotidine. On day 36 he was withdrawn from the study because of severe asthenia and an ALAT of 592. A diagnosis of hepatitis B was established. Eight months later the ALAT was still elevated (450) but no clinical symptoms were present. The investigator concluded that the hepatitis was definitely not drug-related.

A 71 year old man taking several drugs for peripheral vascular disease was randomized to the famotidine treatment group. On day 70 he suffered a myocardial infarction and died within 2 hours. The investigator concluded that this was definitely not drug-related.

A 69 year old man with a history of perforated duodenal ulcer complicated by a right subphrenic abscess was entered into the maintenance trial despite the fact that after 4 weeks of treatment with famotidine 40 mg h.s. in the short-term trial his abdominal pain had not improved and endoscopic examination was not possible because of pyloric deformity. On day 10 the patient was hospitalized for hematemesis and was found to have bronchial carcinoma metastasic to the liver. The investigator concluded that this occurrence was definitely not drug-related.

A 59 year old woman experienced a myocardial infarction on day 24 of treatment with placebo. She subsequently recovered. The investigator assessed this experience as probably not drug-related.

A 56 year old man receiving placebo was found on day 25 to have cancer of colon. The investigator believed that this was definitely not drug-related.

It is obvious from the above summaries that these serious clinical adverse experiences were not drug-related, even though the assessment "probably not" is tantamount to "possibly yes."

(c) Laboratory adverse experiences (table 44): the only noteworthy observation was the occurrence of abnormal results of tests of hepatic injury in 15/255 (6%) of patients receiving famotidine vs 0/271 with placebo. If these numbers are correct, famotidine will bear watching for possible hepatotoxicity; however, none of the changes were serious and only one patient was withdrawn from the study because of a suspect laboratory value. Among the 18 patients 65 years or older receiving famotidine there were no laboratory adverse events.

TABLE 44

Laboratory Adverse Events/Number at Risk

	Famotidine 20 HS N = 306	Placebo N = 339
Hematologic	11/256	10/269
Renal Function	1/151	3/158
Hepatic	15/255	0/271
Metabolic	1/110	2/116
Urogenital	2/258	1/269

(4) Effectiveness

(a) Prevention of recurrence: famotidine significantly decreased the rate and the incidence of recurrence of duodenal ulcer (table 45) compared to placebo. In patients receiving placebo the incidence of recurrence within the first 4 months was an astonishing 60% vs 20% of those receiving famotidine. Data extending to almost 9 months put the incidence of recurrence with placebo (74%) at more than twice that with famotidine; while this is a highly significant difference favoring famotidine, it is far from an impressive achievement, especially since in patients treated with famotidine there was a substantial increase in recurrences from the end of 6 months onward.

TABLE 45

Number of Patients Who Relapsed (%)*
(Life Table Rate)

Months (Day Range) on Treatment	FAMOTIDINE 20 HS (N = 306)	PLACEBO (N = 339)
Month 1 (Days 1-28)	1 (0.3)	21 (6)
Month 2 (Days 29-56)	7 (2)	60 (19)
Month 3 (Days 57-84)	24 (9)	103 (33)
Month 4 (Days 85-112)	50 (19)	185 (62)
Month 5 (Days 113-140)	55 (21)	193 (65)
Month 6 (Days 141-168)	58 (22)	199 (67)
After Month 6 (Days 169-245)	82 (34)	215 (74)

*All Patients Treated Analysis

(b) Relief of pain (table 46): as would be expected from the data on recurrence of ulcers, famotidine was much more effective than placebo in preventing recurrence of ulcer pain. Since patients eligible for admission to the trial were those in whom the ulcer had healed during short-term treatment, the incidence of moderate to severe pain at baseline was negligible. However, the proportion of patients experiencing moderate to severe pain by the end of the study was clearly much greater in patients on placebo than in those on famotidine.

TABLE 46

Distribution of Day and Night Pain

Severity of Pain Baseline	Severity of Pain End of Study	Day Pain Famotidine	Day Pain Placebo	Night Pain Famotidine	Night Pain Placebo
None	None	161	94	192	142
None	Mild	27	56	23	44
None	Mod./Severe	33	115	13	94
Mild	None	26	15	21	10
Mild	Mild	11	7	3	5
Mild	Mod./Severe	8	12	3	3
Mod./Severe	None	2	0	4	2
Mod./Severe	Mild	1	1	0	0
Mod./Severe	Mod./Severe	0	1	0	1

Significant difference between treatments, p<.01, in favor of famotidine for both day pain and night pain.

(c) Antacid consumption: the proportion of patients who took antacids at any time during the trial was significantly higher in patients on placebo (49%) than in those on famotidine (33%), p 0.01. However, the number of doses taken is not reported.

e. Summary: in a multicenter double-blind placebo controlled trial of famotidine 20 mg h.s. (306 patients) vs placebo (339 patients), famotidine was statistically significantly more effective than placebo over a period of 6-9 months in preventing recurrence of duodenal ulcer, relapse of symptoms and requirement for concomitant antacid therapy. Nevertheless, the incidence of recurrence with famotidine, 22% at the end of 6 months, 34% at the end of an additional 3 months, suggests that by the end of a year the incidence of recurrence may well be higher than the 25-35% incidence reported in clinical trials of other drugs.

3. Study No. 5007

a. Title of study: Comparison of famotidine vs placebo in the short-term treatment of gastric ulcer.

b. Design of study: patients with clinical symptoms and endoscopic evidence of a gastric ulcer measuring 0.5-2.5 cm were allocated randomly to receive either famotidine 40 mg or matching placebo at bedtime. Each patient received a bottle of antacid tablets to be taken only if additional symptomatic relief was required. The maximum number of tablets allowed per day had a neutralizing capacity of 88 mEq/day.

Exclusions and procedures at the initial (screening) visit were the same as in the protocol for short-term treatment of duodenal ulcer. Assessment of clinical symptoms and endoscopy were performed at weeks 4, 6 and 8 unless complete healing of the ulcer was demonstrated at the previous visit. At each visit patients were given take-home cards to record day and night pain, number of antacid tablets taken and any adverse experiences. Adverse symptoms and laboratory events were evaluated by the investigator.

An ulcer was considered healed if there was complete epithelization of the crater, regardless of the emergence or persistence of gastritis or erosions. A biopsy was performed at the initial visit, and, at the discretion of the investigator, at subsequent visits, to rule out gastric carcinoma.

Day and night pain and overall therapeutic responses were scored using the same grading system described above in the foreign short-term trial of healing of duodenal ulcer.

Investigators (table 47): the 44 investigators from 14 countries are all qualified by training and experience to conduct a clinical trial of this type.

Table 47

Country/Name	Affiliation	Location
Argentina		
A. Depaula, A.O.F.	Director of the Hospital	Ramos Mejia Hospital, Buenos Aires
Kohan, S.	Chief of Gastroenterology Dept.	Piravana Hospital, Buenos Aires
Segal, J.E.	Chief of Gastroenterology Dept.	Durand Hospital, Buenos Aires
Austria		
Hentschel, E.	Internist	Hanusch Hospital, Vienna
Reichel, W.	Director of Endoscopical Ambulance	Wilhelminen Hospital, Vienna
Schultze, K.	Specialist in Internal Medicine	Hanusch Hospital, Vienna
Brazil		
Castro, L.	Gastroenterologist	Federal University of Minas
Vilela, M.P.	Gastroenterologist	Hospital Sao Paulo
Canada		
Archambault, A.	Head of Gastroenterology	Maisonneuve-Rosemont, Hospital Montreal
Marcon, N.W.	Head of Gastroenterology	The Wellesley Hospital, Toronto
Colombia		
Aponte, L.	Endoscopist/Gastroenterologist	Carrera 18 No. 80-67, Bogota
Denmark		
Rokkjaer, M.	Head Surgeon	Arhus Council Hospital, Arhus
Holland		
Kottner, M.	Internist	Gasthuis Middelburg, Middelburg
Van Bentem	Gastroenterologist	De Stadsmaten Hospital, Ensheda
Wesdorp, I.C.E.	Gastroenterologist	Andreas Hospital, Amsterdam
Italy		
Baglioni, A.	Surgeon, Lecturer	Hospital Generale, Provinciale, "SS Trinita", Sora
Barbara, L.	Director of Gastroenterology	Hospital Sant'Orsola, Bologna
Bianchi-Porro, G.	Director of Gastroenterology	Hospital L. Sacco, Milan
Blasi, A.	Director of Gastroenterology	Hospital Vittorio, Emanuele II, Catania
Carotenuto, F.	Head Surgeon	Municipal Hospital of Cassino
Chelf, R.	Chief of Gastroenterology	Hospital S. Martino, Genova
Dal Monte, P.R.	Head Gastroenterologist	Hospital Bellaria, Bologna
Francaville, A.	Head of Gastroenterology	Cattedra de Malattie, Bari Apparato
Matarazzo, P.F.	Assistant Surgeon	Municipal Hospital of Formia
Mazzacca, G.	Division of Gastroenterology	School of Medicine, Naples
Paoluzi, P.	Gastroenterologist/Endoscopist	II Clinical Medica Universita
Speranza, V.	Head of Surgical Clinic	VI Clinical Chirurgica University
Vagni, V.	Consultant Endoscopist, Lecturer	Municipal Hospital Castellana
Verme, G.	Professor, Head Physician	Hospital Molinette, Torino
Finland		
Pikkarainen, P.	Head of Gastroenterology	University Central Hospital, Kuopio
Krekela, I.	Physician	University Central Hospital, Oulu
France		
Paris, J.C.	Head of Gastroenterology	Centre Hospitalier Regional, Lille
Sarles, H.	Professor, Dept. Head	Hospital of Sante Marseille Marguerite
Germany		
Dammann, H.G.	Head of Gastroenterology	Bethanien Hospital, Hamburg
Jakob, G.	Head of Gastroenterology	District Hospital, Eichstaett
Miederer, S.E.	Professor of Gastroenterology	Medical University Poliklinik, Bonn
Ottenjann, R.	Head of Dept. of Internal Medicine	Municiple Hospital Hue
Paul, F.	Professor, Head of Medical Clinic II	Klinik Ingolstadt, Ingolstadt/Donau
Schuetz, E.	Internist/Gastroenterologist	Gastroenterology-Proktology, Regensburg
Simon, B.	Specialist for Gastroenterology	Medical University, Klinik, Heidelburg
Stadelmann, O.	Head of Gastroenterology	ChA d. Medical Klinik Fuerth
Mexico		
Villalobos, J.	Head of Gastroenterology	National Institute of Nutrition, Mexico, D.F.
South Africa		
Minder, R.A.	Gastroenterologist	Johannesburg Hospital, Parktown
Mel, C.J.C.	Professor, Gastroenterologist	University Hospital, Bloemfontein
Sweden		
Hradsky, M.	Chief of Gastroenterology Unit	Falu Hospital, Falun

d. Results

(1) Comparability of the treatment groups (table 48): case report forms for 336 patients were available by the cut-off date of December 21, 1984, 167 randomized to famotidine, 169 to placebo; the 2 groups were comparable in all respects except that there was a significantly higher (p 0.01) proportion of drinkers among patients in the placebo group.

TABLE 48

Comparability of Treatment Groups

	Famotidine N = 167	Placebo N = 169
Age (yrs)		
Mean	52.2	51.5
Median	55.0	54.0
Sex		
Males	104	104
Females	63	65
Weight (kg)	66.3	66.2
Smoking	98 (59%)	104 (62%)
Alcohol	70* (42%)	100 (57%)
Initial Ulcer Size (cm)[a]		
Mean	1.15	1.06
Median	1.00	1.00
Number of Ulcers		
One	148 (89%)	159 (94%)
Two or more	19 (11%)	10 (6%)
Age at First Ulcer (yrs)		
Mean	48.2	47.2
Median	52.0	47.0
Duration of Ulcer Dis.(yrs)		
Mean	4.0	4.4
Median	0.0	0.0
Ulcer History		
None	85 (51%)	86 (51%)
Single	41 (25%)	37 (22%)
Multiple	41 (25%)	40 (24%)
Other pathology, Esophagus	13 (8%)	11 (7%)
Other pathology, Stomach	61 (37%)	61 (36%)
Other pathology, Duodenum	31 (19%)	29 (17%)

a For patients with more than one ulcer, this was the size of the largest ulcer.
* Significantly different from the placebo group (p 0.01).

(2) Exclusions from analysis of effectiveness (table 49): 11% of the patients randomized to receive famotidine and 14% of those randomized to placebo were excluded for various protocol violations. These percentages are not excessive compared with numbers reported in other NDAs for studies of this type.

TABLE 49

Exclusions from analysis of effectiveness

Reasons	Famotidine N=167	Placebo N=169
Off drug	2	4
Ulcer 2.5 cm	5	3
Ulcer 0.5 cm	3	3
Cancer at entry	1	5
Concomitant medication	3	3
Endoscopy out of range	2	1
Other	2	5
Total (%)	18 (11)	24 (14)

(3) Safety

(a) Vital signs (table 50): the only change in vital signs after treatment was a clinically inconsequential mean weight gain of 0.4 kg in patients on famotidine.

TABLE 50

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE
Pulse rate	Famotidine	161	74.7	74.9	0.2
	Placebo	160	74.7	75.1	0.4
Systolic BP	Famotidine	161	133.0	131.8	-1.2
	Placebo	161	131.8	132.2	0.4
Diastolic BP (mmHg)	Famotidine	159	80.8	80.6	-0.2
	Placebo	159	80.3	81.5	1.2
Weight (kgs)	Famotidine	161	66.3	66.7	0.4MM,*
	Placebo	162	66.2	66.1	-0.1

* Significant difference between treatment groups ($p < 0.05$).
MM Significant increase from baseline ($p < 0.01$).

(b) Adverse signs/symptoms were no more frequent among patients receiving famotidine than among those receiving placebo, totaling 13% of the patients entered in either group (table 51). The proportions considered by the investigators to be possibly/probably drug-related were also the same for each group (famotidine 7%, placebo 6%). The investigators considered withdrawals drug-related in 1 famotidine-treated patient (0.6%) and 5 placebo patients (3%) (table 52). Among the adverse reactions considered serious, 3 occurred in patients receiving famotidine, the first of which was a 55 year old man withdrawn from the study after 29 days of treatment after surgical removal of a melanoma of the skin, the second a 26 year old women withdrawn at the first follow-up visit because endoscopic biopsy revealed multiple granulomatous ulcers compatible with a diagnosis of Crohn's gastritis, the 3rd a 42 year old paraplegic male who had a pulmonary embolism 12 days after entering the trial. The one patient with a serious adverse clinical reaction in the placebo group was a 39 year old man in whom, because the ulcer had not healed at 8 weeks, a biopsy was performed and found to contain carcinoma. Obviously none of these reactions could by any stretch of the imagination be considered drug-related.

TABLE 51

Clinical Adverse Experiences By Body System (%)

	FAMOTIDINE (N = 167)	PLACEBO (N = 169)
Body as a whole	1 (0.6)	3 (1.8)
Cardiovascular	1 (0.6)	1 (0.6)
Central Nervous	1 (0.6)	1 (0.6)
Digestive	9 (5.4)	7 (4.1)
Integumentary	2 (1.2)	3 (1.8)
Metabolic/Nutritional /Immune	2 (1.2)	0 (0.0)
Musculoskeletal	1 (0.6)	2 (1.2)
Nervous and Psychiatric	5 (3.0)	9 (5.3)
Respiratory	5 (2.4)	4 (2.4)
Tegumentary	2 (1.2)	2 (1.2)
Special Senses	1 (0.6)	0 (0.0)
Urogenital	3 (1.8)	2 (1.2)
Total	22 (13.2)	22 (13.0)

TABLE 52

Patients Withdrawn Due to Adverse Experience

TREATMENT GROUP	AN	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	TOTAL POSSIBLY/PROBABLY DEFINITELY
Famotidine 40 HS	39	Disorientation	Severe	Possibly	
		Muscular cramps	Severe	Probably	
		Sexual impotence	Severe	Probably	
	152	Acid regurgitation	Moderate	Definitely Not	
		Fullness	Moderate	Definitely Not	
	205	Skin melanoma	--	Definitely Not	
	293	Gastric granuloma	Severe	Definitely Not	
	310	Development of duodenal ulcer	Mild	Definitely Not	
	316	Pulmonary embolism	Severe	Definitely Not	
		Pneumonia	Severe	Definitely Not	1 (0.6)%
Placebo	63	Asthenia	Mild	Possibly	
	123	Abdominal discomfort	Severe	Definitely	
		Flatulence	Moderate	Definitely	
		Fullness	Severe	Definitely	
		Nausea	Severe	Definitely	
		Vomiting	Severe	Definitely	
	136	Headache	Severe	Probably	
		Nausea	Moderate	Possibly	
		Development of duodenal ulcers	--	Definitely Not	
	197	Nausea	Mild	Probably Not[a]	
		Duodenal ulcer	Moderate	Probably	
		Flatulence	Mild	Probably Not[a]	
		Cold	Mild	Definitely Not	
		Cough	Mild	Definitely Not	
		Fever	Moderate	Definitely Not	
	333	Vomiting	Moderate	Probably Not[a]	5 (3%)

[a]"Probably not" = "Probably"

(c) Laboratory adverse events: there were 5 abnormal laboratory reports in patients receiving famotidine, 6 in patients receiving placebo; none of these were serious or drug-related or necessitated withdrawal of the patients from the trial.

(4) Effectiveness

(a) Incidence of healing (table 53): the cumulative incidence of healing with famotidine was 45% at week 4, 62% at week 6, 77% at week 8, all statistically significantly superior to the incidence of healing in patients receiving placebo (30%, 44% and 51%) at the respective weeks.

TABLE 53

Cumulative Number Healed/Number Entered (%)

Week	Endoscopic Range, Days	Famotidine n=167	Placebo n=169	p
4	Up to 34	75 (45)	50 (30)	<0.01
6	35 to 49	104 (62)	74 (44)	<0.01
8	50 to 64	128 (77)	86 (51)	<0.01
Later	After 64	131 (78)	88 (52)	<0.01

(b) Relief of pain: the proportion of patients relieved of day pain (figure 42) was clearly higher in those receiving famotidine at all intervals from the first day of treatment through the end of the 8th week. By the end of the first week day pain was relieved in some 40% of patients on famotidine vs 20% in patients on placebo; by the end of the study the difference in the proportion of patients without day pain had narrowed between the 2 treatment groups to 80% vs some 65% respectively. With regard to night pain very little difference was evident between the 2 groups (figure 43). In patients receiving famotidine the median number of days to relief of both day and night pain was proportional to the severity

Figure 42
Percentage of Patients With No Day Pain

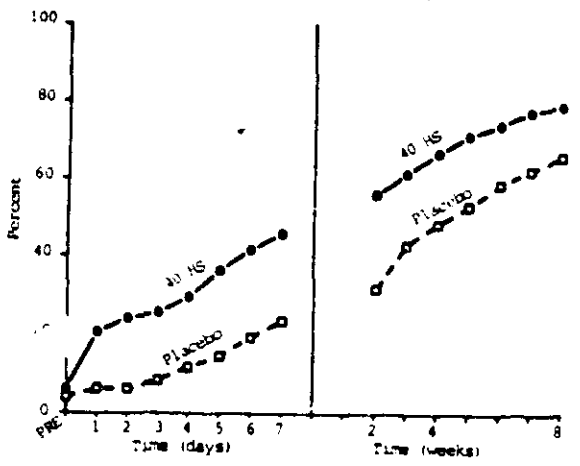
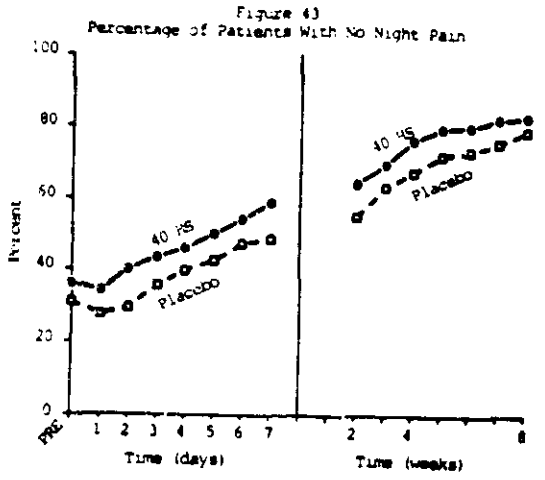


Figure 43
Percentage of Patients With No Night Pain



of pain at the outset; this was not the case in patients receiving placebo (table 54). In patients receiving famotidine, the median number of days to relief of both day and night pain was 5 in patients starting with mild pain, 14 in patients starting with moderate pain and 28 in patients starting with severe pain.

TABLE 54
Time to Relief of Pain

		FAMOTIDINE (N=149)	PLACEBO (N=145)
	Day Pain		
Baseline =	None[a]	1.0 (n = 9)	21.5 (n = 6)
	Mild	5.0 (n = 31)	31.5 (n = 32)
	Moderate	14.0 (n = 68)	35.0 (n = 80)
	Severe	28.0 (n = 41)	35.0 (n = 47)
	All**	14.0 (n = 149)	35.0 (n = 145)
	Night Pain		
Baseline =	None	1.0 (n = 56)	1.0 (n = 45)
	Mild	5.5 (n = 22)	18.0 (n = 30)
	Moderate	14.0 (n = 47)	21.0 (n = 41)
	Severe	28.0 (n = 26)	28.0 (n = 29)
	All**	5.0 (n = 149)	14.0 (n = 145)

[a] Some patients had no pain at baseline but had pain at one or more subsequent timepoints.
** Significant difference between treatment groups ($p < 0.01$)

(c) Antacid consumption: the percentage of patients taking antacids (figure 44) was quite high in both groups, but at all intervals was higher in patients on placebo than in those on famotidine. Since there are no data on the number of antacid doses taken, it is not known whether there is any clinical significance in these differences. The average number of days of antacid consumption (table 55) was statistically but not clinically significantly higher with placebo.

Figure 44
Percent of Patients Receiving Antacid Therapy

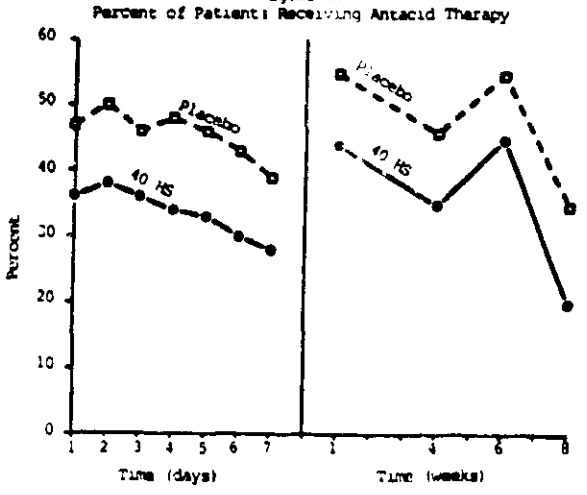


TABLE 55
Antacid Consumption
Mean Days of Antacid Therapy, Mean ± Standard Deviation

	Famotidine 40 HS			Placebo			Number of Days Difference Between 40 HS and Placebo
WEEK	N	MEAN		N	MEAN		
1	149	2.4	± 3.0*	145	3.2	± 3.2	-0.8
4	142	1.7	± 2.8*	137	2.7	± 3.2	-1.0
6	135	1.4	± 2.6*	129	2.1	± 3.0	-0.7
8	36	1.4	± 2.7*	48	2.2	± 3.2	-0.8

*Significantly different from the placebo group ($p < 0.05$).

(d) Patients global assessments (table 56): a remarkable observation is that good to excellent relief of symptoms at 4, 6 and 8 weeks respectively was reported by 64%, 70% and 74% of patients receiving placebo treatment. Nevertheless, an equal degree of symptomatic relief was reported in a sufficiently higher number of individuals receiving famotidine that the results with the drug were statistically significantly better than with placebo.

TABLE 56

Patients Global Assessments

TIMEPOINT	ASSESSMENT	FAMOTIDINE		PLACEBO	
		#	%	#	%
Week 4	Excellent/Good	109	80	85	64
	Fair/Poor/None	28	20	48	36
	Total*	137		133	
Week 6	Excellent/Good	125	86	99	71
	Fair/Poor/None	20	14	41	29
	Total*	145		140	
Week 8	Excellent/Good	127	88	102	73
	Fair/Poor/None	18	12	38	27
	Total*	145		140	
All Patients Treated	Excellent/Good	141	87	111	70
	Fair/Poor/None	21	13	47	30
	Total*	162		158	

*Significantly better distribution for the famotidine group than for the placebo group ($p < 0.01$)

4. Study No. 746

a. Title of study: Comparison of famotidine vs Gefarnate in the short-term treatment of benign gastric ulcer.

[Gefarnate is a long-chain unsaturated fatty acid marketed in Japan, among other countries, for the treatment of gastric ulcer. In the sponsor's opinion it is tantamount to a placebo.]

b. Design of study: in this multi-center, double-blind, randomized, active control trial patients with endoscopic evidence of a single-gastric ulcer, circular or oval in shape, were assigned to receive either famotidine 20 mg b.i.d. or Gefarnate 100 mg t.i.d. Matching placebos were taken at appropriate times utilizing a double-dummy technique. Antacid was supplied for relief of ulcer pain as necessary. Each dose was equivalent to 0.6 gm of dried aluminum hydoxide gel and the frequency of dosing was limited to 10 times per week.

Exclusion criteria included ulcers of the pyloric channel and esophagogastric junction, a history of gastric surgery (including vagotomy), nursing, confirmed or suspected pregnancy, or severe concurrent disease.

Baseline evaluation consisted of history, physical examination, laboratory studies, gastric endoscopy and biopsy. Physical examination and laboratory studies were repeated at weeks 4 and 8.

Healing was defined as complete epithelization, regardless of associated gastritis or erosions.

c. Investigators (table 57): investigators at 32 Japanese centers participated.

Table 57

Country/Name	Affiliation	Location
Japan		
Yachi, Akira	Internist	Sapporo Medical College, Sapporo, Hokkaido
Ishimori, Akira	Gastroenterologist	Tohoku University, Sendai-shi, Miyagi Pref.
Sekiguchi, Toshikazu	Internist	Gunma University, Maebashi-shi, Gunma Pref.
Sakita, Takao	Internist	The University of Tsukuba, Tokyo Niihari-Gun, Ibaraki Pref.
Kitamura, Tatsuya	Internist	University of Tokyo, Bunkyo-ku, Tokyo
Takeuchi, Tadashi	Gastroenterologist	Tokyo Women's Medical Coll., Shinjuku-ku, Tokyo
Omata, Shozo	Gastroenterologist	Yokohama Shimin Hospital, Hodogaya-ku, Kanagawa Pref.
Honda, Toshio	Internist	Nihon University, Kanda Chiyoda-ku, Tokyo
Imeda, Noritzugu	Gastroenterologist	Nat'l Medical Center Hosp., Shinjuku-ku, Tokyo
Hongo, Hoshio	Internist	Icho Hospital, Shinjuku-ku, Tokyo
Kubota, Yuzuru	Internist	St. Luke's Int'l Hospital, Chuo-ku, Tokyo
Takasu, Sachio	Gastroenterologist	Kanto Teishin Hospital, Shinagawa-ku, Tokyo
Tsuchiya, Masahara	Gastroenterologist	Keio University, Shinjuku-ku, Tokyo
Sugata, Fumio	Gastroenterologist	Showa University, Yokohama, Kanagawa Pref.
Okabe, Haruya	Internist	Kitasato University, Sagamihara-shi, Kanagawa Pref.
Mima, Takeshi	Internist	Tokai University, Isehara-shi, Kanagawa Pref.
Okabe, Kazuhiko	Gastroenterologist	St. Marianna University, Kawasaki-shi, Kanagawa Pref.
Watanabe, Yozo	Surgeon	Juntendo University, Bunkyo-ku, Tokyo
Kaneko, Eizo	Internist	Hamamatsu University, Hamamatsu-shi, Shizuoka Pref.
Nakazawa, Saburo	Internist	Nagoya University, Nagoya, Aichi Pref.
Takeuchi, Toshihiko	Internist	Nagoya City University, Nagoya, Aichi Pref.
Suyama, Tetsuji	Gastroenterologist	The Ctr. for Adult Diseases, Moriyama-shi, Shiga Pref.
Uchino, Haruto	Internist	Kyoto University, Kyoto-shi, Kyoto
Kawai, Keiichi	Internist	Kyoto Prefectural University, Kyoto-shi, Kyoto
Yukawa, Eiyo	Gastroenterologist	Yukawa Icho Hospital, Tennoji-ku, Kyoto
Shimoyama, Takashi	Internist	Hyogo College of Medicine, Nishinomiya, Hyogo Pref.
Kita, Shoichi	Internist	Kawasaki Medical College, Okayama-shi, Okayama Pref.
Ohe, Keiji	Internist	Hiroshima University, Hiroshima-shi, Hiroshima Pref.
Mori, Hiroyoshi	Gastroenterologist	University of Tokushima, Tokushima-shi, Tokushima Pref.
Misawa, Tadashi	Internist	Kyushu University, Fukuoka-shi, Fukuoka Pref.
Inoue, Mikio	Internist	Fukuoka University, Fukuoka-shi, Fukuoka Pref.
Yunoki, Kazuo	Internist	Kagoshima University, Kagoshima-shi, Kagoshima Pref.

d. Results

(1) Comparability of treatment groups (table 58): there were 96 patients in each group; the 2 groups were comparable in all essential respects.

(2) Exclusions from analysis of effectiveness (table 59): almost all of the 23% of patients lost to analysis were a result of failure to start therapy within 6 days of the baseline endoscopy; this left for analysis 72 patients in the famotidine group, 75 in the Gefarnate group.

(3) Safety

(a) Vital signs (table 60): neither drug had any effect on vital signs.

TABLE 58

Comparability of Treatment Groups at Baseline

	Famotidine 20 BID N = 96		Gefarnate 100 TID N = 169	
Age (years)				
Mean	47.5		46.1	
Median	48.0		48.0	
Sex				
Males	75	(78%)	72	(75%)
Females	21	(22%)	24	(25%)
Initial Ulcer Size (cm)[a]				
Mean	1.4		1.4	
Median	1.2		1.3	
Age at First Ulcer (years)				
Mean	46.0		44.5	
Median	47.0		45.0	
Duration of Ulcer Disease (years)				
Mean	1.5		2.2	
Median	0.0		0.0	
Ulcer History				
None	58	(60%)	55	(57%
Single	15	(16%)	19	(20%
Multiple	23	(24%)	22	(23%
In/Out Patient Status				
In-Patient	5	(5%)	8	(8%)
Out-Patient	91	(95%)	88	(92%)
Prior Ulcer Therapy (within 7 days)	24	(25%)	23	(24%)

a Although only patients with single ulcers were allowed by protocol, some patients with multiple ulcers were entered. For patients with more than one ulcer, this was the size of the largest ulcer. For these patients, all ulcers must have healed to be considered healed

TABLE 59

Exclusions from Analysis of Effectiveness

	Famotidine 20 BID	Gefarnate 100 TID
Off Drug	1	1
Concomitant Drug	1	1
Endoscopy missing or out of range	22	19
TOTAL	24 (25%)	21 (22%)

TABLE 60

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE FROM BASELINE
Body weight (kg)	Famotidine 20 BID	28	72.6	72.0	-0.4
	Gefarnate 100 TID	29	72.4	70.2	-2.2
Pulse (beats/min)	Famotidine 20 BID	23	55.6	56.2	+0.6
	Gefarnate 100 TID	24	55.0	55.6	+0.6
Systolic BP (mmHg)	Famotidine 20 BID	46	122.3	122.8	+0.5
	Gefarnate 100 TID	46	122.2	120.4	-1.8
Diastolic BP (mmHg)	Famotidine 20 BID	46	76.7	75.0	-0.7
	Gefarnate 100 TID	46	75.3	73.8	-1.5

(b) Clinical adverse experiences: drug-related adverse symptoms occurred in 5 patients receiving famotidine, 17 receiving Gefarnate (table 61). The most commonly reported adverse symptoms were constipation, occurring in 4 (4.2%) of the patients and nausea, occurring in 2 (2.1%) in each group. Two serious clinical adverse experiences occurred in each of the treatment groups, gastric cancer and a cerebral vascular accident in the famotidine group, gastric cancer and gastrointestinal bleeding in the Gefarnate group. Of these, only the case of hemorrhage was considered possibly drug-related. Two patients in addition to these, both receiving Gefarnate, were withdrawn because of adverse experiences (table 62), one because of diarrhea/nausea, the other because of weight loss, both considered possibly/probably drug-related.

TABLE 61

Drug-Related* Clinical Adverse Experience

ADVERSE EXPERIENCE	FAMOTIDINE		GEFARNATE	
Body as a Whole	0		0	
Abdominal Pain		0		1
Digestive System	5		15	
Anorexia		0		4
Constipation		3		3
Diarrhea		1		3
Eructation		0		2
Flatulence		1		2
Gastrointestinal Hemorrhage		0		1
Heartburn		0		2
Nausea		2		2
Vomiting		1		0
Peptic Ulcer		0		1
Metabolic/Nutritional System	0		1	
Weight Loss		0		1

*"Possibly", Probably" or "Definitely" related to test drug in investigator's opinion. Total numbers represent counts of patients, not counts of adverse experiences.

TABLE 62

Patients Withdrawn Due to Adverse Experience

TREATMENT	NO.	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	POSS/PROB
Famotidine (n=96)	183	Stomach Cancer	Severe	Definitely Not	
	624	CVA	Severe	Probably Not[a]	1
Gefarnate (n=96)	102	Gastrointestinal bleeding	Severe	Possibly	
	211[b]	Diarrhea/Nausea	Moderate	Possibly	
	262[b]	Weight Loss	Severe	Probably	
	292	Gastric Cancer	Severe	Definitely Not	3

[a] "Probably Not" = "Possibly"
[b] Also considered protocol violators

(c) Laboratory adverse events: 15 patients receiving famotidine and 14 receiving Gefarnate were found to have abnormal laboratory values; none resulted in withdrawal from the trial. Of the 2 events considered serious, a patient on famotidine developed thrombocytopenia (probably not drug-related) and one on Gefarnate had a drop in hemoglobin and red cell count (considered drug-related).

(4) Effectiveness

(a) Incidence of healing (table 63): at all 3 intervals evaluated (4 weeks, 8 weeks and later than 8 weeks) the incidence of healing with famotidine was statistically significantly superior to that with Gefarnate. The final incidence of healing with famotidine was 54/72 (75%), with Gefarnate 23/75 (31%). This is not an impressive record for famotidine considering that the incidence of healing at 8 weeks, 46/72 (64%), was much less than that (77%) in the European multi-center trial. However, judging from my experience with Japanese patients in Hawaii, gastric ulcer may be a different disease in Japanese than in occidentals.

TABLE 63

Cumulative number healed/number evaluable (%)

Week	Endoscopic range, days	Famotidine N=72	Gefarnate N=75	p
4	Up to 32	19 (26)	3 (4)	0.01
8	33 to 60	46 (64)	18 (24)	0.01
Later	61 to 124	54 (75)	23 (31)	0.01

(b) Relief of pain (figure 45): the percentage of patients relieved of pain was statistically significantly higher in patients receiving famotidine at the end of 1 week (2-8 days), 2 weeks (9-15 days) and 4 weeks (16-32 days). Thereafter the percentage of patients relieved of pain was approximately 90% with both treatments.

(c) Antacid consumption (figure 46): during the first 4 weeks the percentage of patients taking antacids was far less in patients receiving famotidine. After 4 weeks none of the patients receiving famotidine were taking antacids, while 10-20% of those receiving Gefarnate were continuing to do so.

Figure 45
Percentage of Patients With No Pain

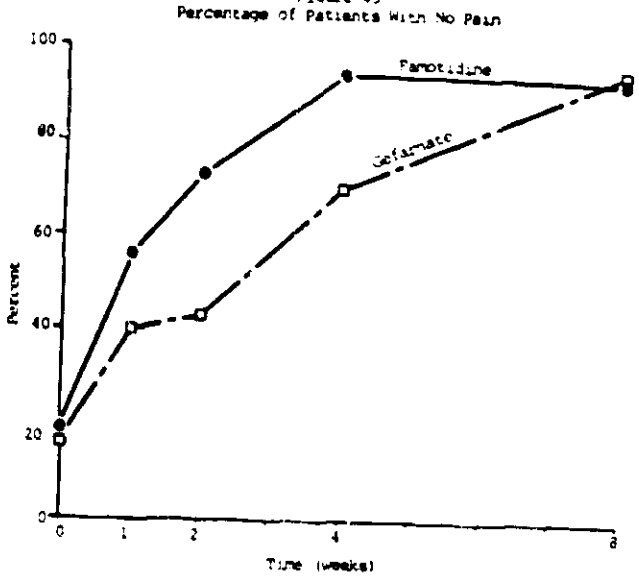
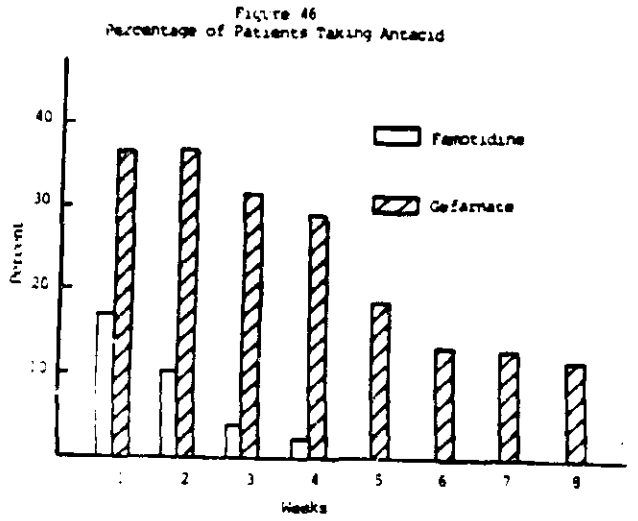


Figure 46
Percentage of Patients Taking Antacid



(d) Investigators' global evaluations (table 64): the data show that the incidence of symptomatic relief greatly exceeds the incidence of healing, confirming what has long been an article of faith in the annals of peptic ulcer disease.

TABLE 64

Investigators' Global Evaluation

Cumulative number markedly improved/number evaluable (%)

Marked Improvement	Famotidine	Gefarnate	p
Week 4	55/76 (72)	17/80 (21)	0.01
Week 8	65/77 (84)	31/79 (39)	0.01

IV. Summary of NDA 19-462

A. Clinical pharmacology: famotidine was well-tolerated in volunteer subjects in doses at least twice the oral and intravenous recommended therapeutic doses. No serious adverse events, either in the form of symptoms or laboratory value deviations were encountered. Bioavailability was in the range of 40-45%. The half-life of the drug was of the order of 3 hours. Famotidine administered orally suppressed pentagastrin-stimulated gastric acid secretion in a dose-related fashion. The acid inhibiting effect of famotidine 5 mg was equivalent to that of cimetidine 300 mg. Twelve hours after administration of famotidine 20 mg, inhibition of pentagastrin-stimulated acid ranged from 18 to 88% with a mean of 54%. Doses of 20 or 40 mg b.i.d. suppressed nocturnal acid secretion more than

90% and meal-stimulated secretions an average of 41% and 57% respectively. A single-dose of 40 mg at bedtime inhibited nocturnal acid secretion, with a carryover effect on the acid response the next morning's breakfast meal. No cumulative effect was observed when famotidine was given over a period of 5 days. Doses of 20 or 40 mg given at bedtime inhibited breakfast, but not lunch- or dinner-stimulated acid secretion. An additional dose given following breakfast did reduce the acid response to the noon meal. The results of these tests of the effect of famotidine on acid secretion were the basis of the decision to include doses of 40 mg h.s., 20 mg b.i.d. and 40 mg b.i.d. in clinical trials of healing of duodenal ulcer.

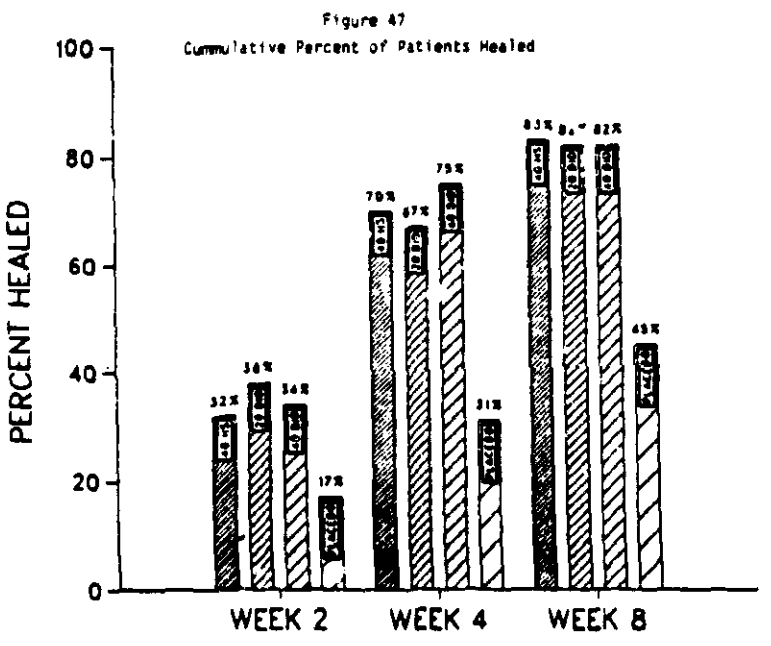
Blood levels of prolactin, FSH, LH, and testosterone were not altered by administration of famotidine; there was a slight increase in serum gastrin. In a study designed to evaluate the effect of famotidine on hepatic metabolic function, famotidine did not induce changes in elimination of aminopyrine or antipyrine in most subjects. The significance of this observation was tested in drug-interaction studies. the results of which indicated that famotidine does not alter the pharmacokinetics of theophylline, warfarin, phenytoin or diazepam.

B. Effectiveness

1. Short-term treatment of duodenal ulcer

a. Incidence of healing: 2 multi-center trials evaluated the incidence of healing with 3 dosage regimens of famotidine (40 mg h.s., 20 mg b.i.d., and 40 mg b.i.d.) one a United States trial comparing famotidine with placebo, the other an International trial comparing famotidine with ranitidine. In both trials the patients were endoscoped at 2, 4 and 8 weeks, the last endoscopy being at the first interval of healing, i.e. in the analysis of the cumulative incidence of healing, a patient whose ulcer was found to be healed at 2 weeks was considered to be healed at 8 weeks. The patients were given diary cards for recording episodes of pain and number of antacid doses taken. In the United States trial 34 investigators entered a total of 384 patients approximately equally distributed among the 4 treatment groups. All of the doses of famotidine were statistically significantly superior to placebo (figure 47); the incidence of healing with the recommended dose of 40 mg h.s. at 4 and 8 weeks was 70% and 83% vs 31% and 45% with placebo (p 0.01). In the International trial 68 investigators entered a total of 1,031 patients with approximately equal numbers in the 4 treatment groups. The

Figure 47
Cumulative Percent of Patients Healed



incidence of healing (figure 48) with famotidine 40 mg h.s. at 4 weeks (68%) was less than that with ranitidine 150 mg b.i.d. (76%) but at 8 weeks they were equal (87% vs 90%). Comparing the results of the U.S. and International trials (table 65) the incidence of healing was the same with the dose of 40 mg h.s., but with the b.i.d. doses the incidence of healing was higher in the International trial at both 4 and 8 weeks.

Figure 48
Cumulative Percent of Patients Healed

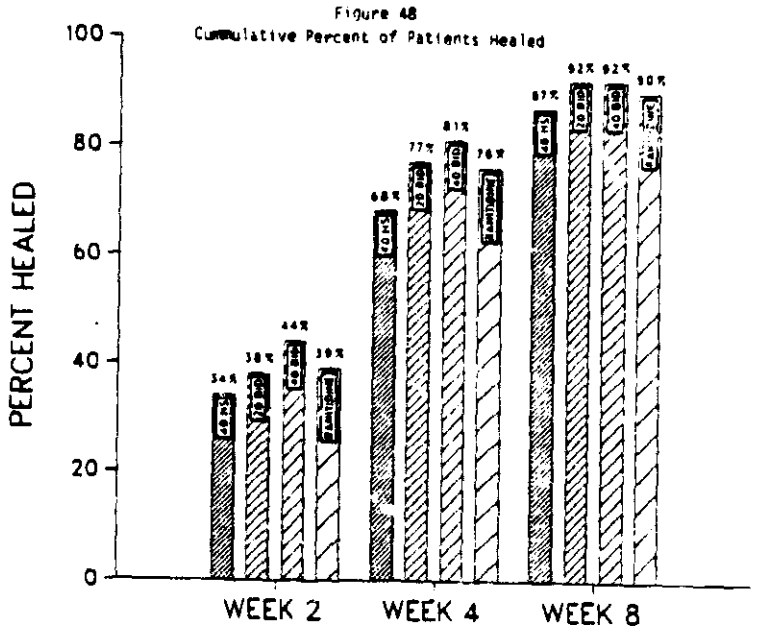


TABLE 65
Cumulative Percent Healed, US & International Trials

Weeks	40 HS n_1	40 HS n_2	40 HS % Healed	20 BID n_1	20 BID n_2	20 BID % Healed	40 BID n_1	40 BID n_2	40 BID % Healed	Placebo n_1	Placebo n_2	Placebo % Healed	Ranitidine n_1	Ranitidine n_2	Ranitidine % Healed
2															
US	96	89	32	89	84	38	99	93	33	100	97	17			
Int*	255	240	34	259	247	38	258	241	44				259	246	39
4															
US			70			67			74			31			
Int			68			77			81						76
8															
US			83			82			81			45			
Int			87			92			92						90

n_1 = number entered
n_2 = number evaluable

*International multicenter trial

b. Relief of pain: ulcer pain was relieved sooner and in a higher percentage of patients receiving famotidine than in those receiving placebo. When compared with ranitidine, pain relief with famotidine was not significantly different.

c. Antacid consumption: in the U.S. study the number of days on which antacids were taken, the number of antacid tablets taken and the percentage of patients taking antacids all favored famotidine over placebo by statistical analysis, but the differences were not clinically meaningful.

2. Prevention of recurrence of duodenal ulcer: the role of famotidine in the prevention of recurrence of duodenal ulcer was evaluated in 2 multicenter, placebo-controlled trials in patients whose ulcers had healed during the short-term treatment were eligible for admission to a trial of famotidine vs placebo in the prevention of recurrence of ulcer. In the U.S. trial 26 investigators entered 177 patients, 54 on 40 mg h.s., 57 on 20 mg h.s. and 66 on placebo. The incidence of recurrence at all intervals up to 6 months (figure 49), which was the cutoff time for analysis of the data, was significantly lower with famotidine. At 6 months the incidence with 40 mg h.s. was 30%, with 20mg h.s. 26%, with placebo 70%. The incidence of recurrence with 20 mg h.s. was not statistically significantly different from that with 40 mg h.s. In the International trial, 64 investigators entered 471 patients, 237 on 20 mg h.s. and 234 on placebo. The incidence of recurrence (figure 50) on both placebo and famotidine was similar to that in the U.S. trial. Thus, in both trials, the recommended dose of famotidine for prevention of recurrence (20 mg h.s.) was statistically significantly superior to placebo (Table 66).

Figure 49
Cumulative Incidence of Relapse (%)

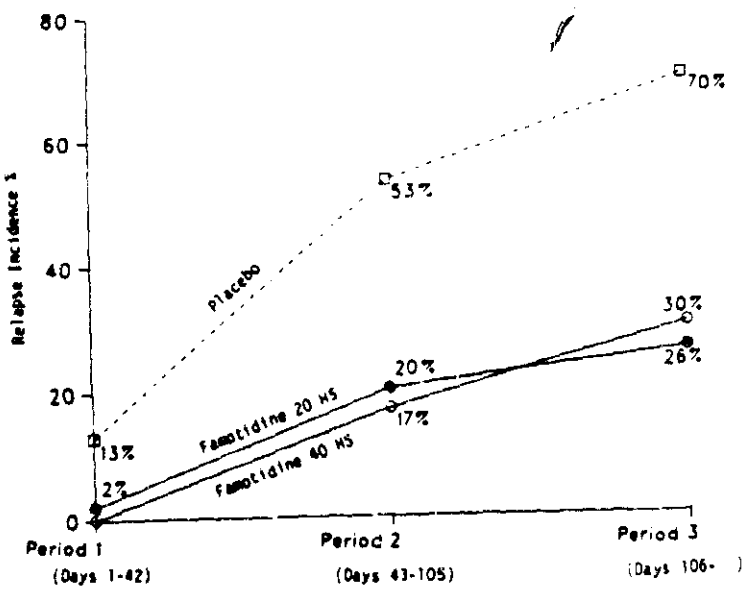


Figure 50
Cumulative Incidence of Relapse (%)

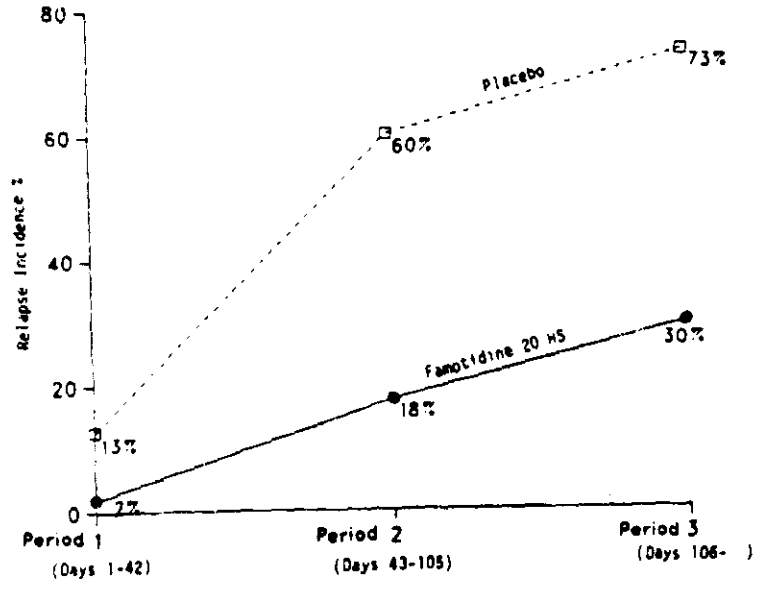


TABLE 66

Cumulative Life-Table Incidence of Recurrence (%)
U.S. and International Trials

	40 MS N	40 MS % Recurred	20 MS N	20 MS % Recurred	Placebo N	Placebo % Recurred	P
Days 1-42							40 MS: 20: <0.01 <0.05 PLA; 20: <0.01
U.S.	54	0	57	1.8	56	12.1	
International			268	1.9	306	12.7	
Days 43-105							40 MS: 20: <0.01 <0.01 PLA; 20: <0.01
U.S.	46	15.2	49	17.9	47	51.4	
International			237	17.6	234	60.1	
Days 106 or later							40 MS: 20: <0.01 <0.01 PLA; 20: <0.01
U.S.	22	30.6	32	25.5	19	66.7	
International			182	29.6	95	73.1	

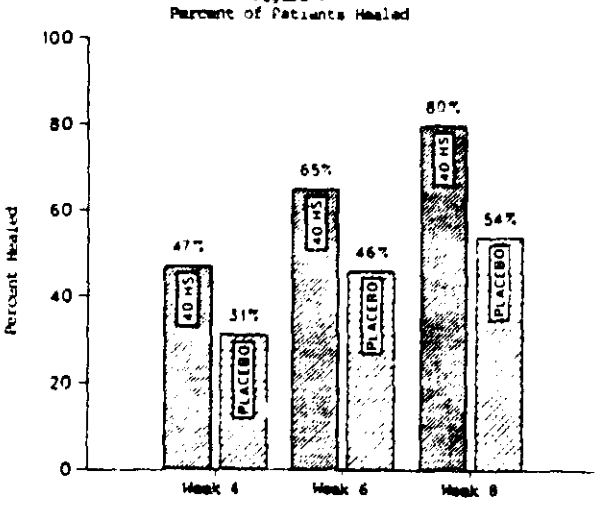
3. Treatment of gastric hypersecretory conditions: two studies were conducted in the United States on small series of patients with gastric acid secretion in the pathological range, all with suspected or proven Zollinger-Ellison syndrome. These patients had previously been treated with either cimetidine or ranitidine or both. The mean minimum daily doses expressed as grams/day required to suppress gastric acid secretion to less than 10 mEq/h during the 6 hours after administration of the drugs were famotidine 0.24, ranitidine 2.1 and cimetidine 7.8. Besides greater potency famotidine also had a longer duration of action than either of the other two H_2-blockers. Like ranitidine, but in contrast to cimetidine, famotidine was not associated with anti-androgenic side-effects. There is as yet no evidence that the higher potency and longer duration of action of famotidine will translate into dosage intervals less than 6 hours for adequate control of the gastric acid output.

4. Short-term treatment of gastric ulcer:

a. International multi-center trial: the only placebo controlled trial of famotidine in the short-term treatment of gastric ulcer was conducted in 14 countries with the participation of 44 investigators. A total of 336 patients were entered, 167 on famotidine 40 mg h.s., 169 on placebo.

(1) Incidence of healing: the proportion of patients whose ulcers healed was statistically significantly greater at all time intervals (4, 6 and 8 weeks) in patients receiving famotidine than in those receiving placebo (p 0.01)(figure 51). The incidence of healing with famotidine at the respective intervals was 47%, 65% and 80% in contrast to the respective percentages of 31, 46 and 54 with placebo.

Figure 51
Percent of Patients Healed



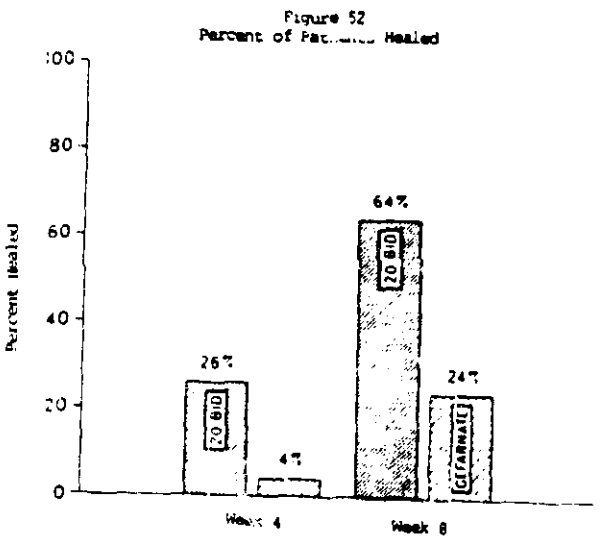
(2) Relief of pain: both day and night pain were more rapidly relieved in patients receiving famotidine.

(3) Antacid consumption: concomitant use of antacids was statistically significantly lower for patients treated with famotidine, but the difference was not enough to be of clinical importance.

(4) Patients' assessment of global response: at all time points patients in both groups claimed good to excellent symptomatic response in statistically significantly higher proportions than those who rated their responses as fair, poor or none, and in significantly higher proportions in patients receiving famotidine than in those receiving placebo.

2. Japanese clinical trial: the procedure was essentially the same as that in the International multi-center study except that the comparison was between famotidine 20 mg b.i.d. and Gefarnate 100 mg t.i.d. Investigators from 32 centers in Japan contributed a total 192 patients, 96 in each of the treatment groups. The incidence of healing of the gastric ulcers (figure 52) was much lower in the patients receiving famotidine than was the case in the International multi-center trial, possibly because the dosage of famotidine used in this trial (20 mg b.i.d.) is not comparable to that in the International trial (40 mg h.s.) and possibly because in the Japanese population gastric ulcer is a more resistant disease. The incidence of healing with famotidine vs Gefarnate was 25% vs 4% at 4 weeks and 64% vs 24% at 8 weeks.

Figure 52
Percent of Patients Healed



The percentage of patients without pain was statistically significantly higher at all time points up to, but not including, 8 weeks in patients receiving famotidine. The percentage of patients taking antacids was significantly less with famotidine than with Gefarnate. Antacids were not required after the 4th week in patients on famotidine, but continued to be required in approximately 15% of patients taking Gefarnate up to 8 weeks.

V. Safety

Safety data updated to November 18, 1985 were available from 2,333 patients in world-wide trials. The most common clinical adverse experiences are headache (4.7%), diarrhea (1.7%), nausea (1.5%), constipation (1.3%) and dizziness (1.2%). The laboratory data indicate no evidence of serious drug-related hematological, hepatic or renal toxicity. The safety profile of famotidine will only become apparent, however, in the market place.

There were 19 deaths in the world-wide experience, none of them drug-related (table 67), only 3 of which occurred in patients treated for indications addressed in this NDA.

TABLE 67

Deaths in Patients Treated with famotidine

Ident.	Age	Sex	Immediate Cause	Concurrent Condition	Route of Administration	Indication
				JAPAN		
Japan	24	M	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
Japan	41	M	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
Japan	44	F	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
Japan	55	M	Hepatic failure	GI hemorrhage fulminant hepatitis	I.V.	stress ulcer
Japan	68	M	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
2103	Unk*	Unk	Unknown	GI bleeding/stress ulcer; Colon cancer	I.V.	stress ulcer
2104	Unk	Unk	MI**; Renal failure	GI hemorrhage/stress ulcer; MI (past)	I.V.	stress ulcer
2105	Unk	Unk	Respiratory failure	GI hemorrhage/stress ulcer; Colon cancer Renal insufficiency	I.V.	stress ulcer
0704	Unk	Unk	Unknown	GI hemorrhage/stress ulcer; Perforation of stomach; Rheumatoid arthritis	I.V.	stress ulcer
2501	72	M	Hepatic failure	GI hemorrhage/stress ulcer; Hepatoma; Subphrenic abscess	I.V.	stress ulcer
2702	58	M	Hepatic failure	GI hemorrhage/stress ulcer; Pancreatitis; Liver cancer; Cirrhosis; Cholelithiasis	I.V.	stress ulcer
3602	62	M	Unknown	GI hemorrhage/stress ulcer; Bladder cancer	I.V.	stress ulcer
				INTERNATIONAL		
1895	71	M	Myocardial Infarction	—	oral	maintenance therapy
71R	44	M	Peritinitis	Cirrhosis of liver	I.V.	stress ulcer
2005	86	F	Respiratory failure	Pneumonia	oral	peptic ulcer
709	46	F	Septicemia	Third degree burns on 60% of body; pneumonia	I.V.	stress ulcer
718	23	M	Brain infarctions	—	I.V.	stress ulcer
7C0	75	F	Abdominal infection	Vovulus of small bowel with necrosis	I.V.	stress ulcer
				U. S.		
3	64	F	"Natural"	—	oral	Zollinger-Ellison Syndrome

*Unk = Unknown
**MI = Myocardial infarction

VI. Package insert: the insert (attached) is generally factually correct but is unnecessarily repetitive. I have indicated my suggestions for revision.

VII Conclusions

A. Pepcid (famotidine) is safe and effective in the following dosage for the following indications:

1. 40 mg h.s. for the short-term (4-8 weeks) treatment of duodenal ulcer.

2. 40 mg h.s. for the short-term (4-8 weeks) treatment of gastric ulcer.

3. 20 mg q 6h initially and increased as necessary to reduce gastric acid output below 10 mEq/hr in the treatment of Zollinger-Ellison syndrome.

B. Data from 2 6-month trials of prevention of recurrence of duodenal ulcer show that famotidine is more effective than placebo but do not provide a sufficiently long follow-up (at least one year) to permit a final assessment of the effectiveness of famotidine for this indication.

VIII Recommendations: Approve the application for the following indications and dosages:

1. 40 mg h.s. in the short-term (4-8 weeks) treatment of duodenal ulcer.

2. 40 mg h.s. in the short-term (4-8 weeks) treatment of gastric ulcer.

3. 20 mg q 6 h, increased as necessary to keep gastric acid output below 10 mEq/hr in the treatment of Zollinger-Ellison syndrome.

William H. Bachrach

William H. Bachrach, M.D.

cc: Orig. NDA 19-462
HFN-110
[redacted]
HFN-110/WHBachrach
rq:12-21-85:12-26:12-30:0409r

A.H.F.S. Category: 56:40

MSD| Tablets PEPCID™ XXXXXXX
(Famotidine, MSD)

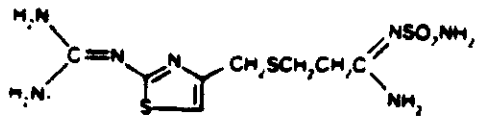
PEPCID™
(Famotidine, MSD)

DESCRIPTION[1]

The active ingredient in Tablets PEPCID* (Famotidine, MSD), is a histamine H_2 receptor antagonist.

Famotidine is 3-[[[2-[(aminoiminomethyl) amino]-4-thiazoyl] methyl]thio]-N-(aminosulfonyl) -propanimidamide.

The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.43. Its structural formula is:



Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc, titanium dioxide.

1. Chemistry, Manufacturing and Controls
**Item II. D. 1. Vol. 1.1, p. 25
Item III. A. B. Vol. 1.2, p. 08

** All annotations will have two references. The first reference is to Item II-Summary of Application contained in this volume. The page number indicates where a brief description can be found. The second reference is to a specific technical section and gives the volume and page number where a detailed description can be found.

PEPCID™
(Famotidine, MSD)

CLINICAL PHARMACOLOGY

GI Effects: PEPCID is a competitive inhibitor of histamine H_2-receptors.[2] The primary clinically important pharmacologic activity of PEPCID is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by PEPCID,[3] while changes in pepsin secretion are proportional to volume output.[4]

In both normal volunteers and hypersecretors, PEPCID inhibited basal, nocturnal[3,7] and daytime gastric secretion,[3,5] as well as secretion stimulated by ~~a variety of stimuli, such~~ as pentagastrin[4,6,8] ~~and food.[3,8]~~ After oral administration, the onset of the antisecretory effect occurred within one hour;[3,4,5,7] the maximum effect was dose-dependent, occurring within one to three hours.[3,4,6] Duration of inhibition of secretion was 10 to 12 hours.[3,7] After intravenous administration, the maximum effect was achieved within 30 minutes.[8] Single oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects; mean gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours.[3] Similar doses given in the morning

2. Preclinical Pharmacology
   Item II. D. 2. Vol. 1.1, p. 29
   Item IV. A. 1. Vol. 1.3, p. 01

3. Ryan Study No. 8
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1819

4. Smith Study No. 2
   Item II. D. 4. Vol. 1.1, p. 87
   Item VII. F. 1. a. ii. Vol. 1.31, p. 1518

5. Ryan Study No. 7
   Item II. D. 4. Vol. 1.1, p. 88
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1748

6. McCallum Study No. 3
   Item II. D. 4. Vol. 1.1, p. 87
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1583

7. Cohen Study No. 5
   Item II. D. 4. Vol. 1.1, p. 88
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1668

8. Hunt Study No. 725
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1917

PEPCID™
(Famotidine, MSD)

CLINICAL PHARMACOLOGY (cont'd)

suppressed food-stimulated acid secretion in all subjects, with mean suppression of 76% and 84%, respectively, 3 to 5 hours after drug, and of 25% and 30%, respectively, 8 to 10 hours after drug; however, in some subjects who received the 20 mg dose, the antisecretory effect was dissipated earlier, within 6-8 hours.[9] There was no cumulative effect with repeated doses.[10] The basal nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of PEPCID to mean values of 5.0 and 6.4, respectively.[9,11] When PEPCID was given in the morning, the ~~basal~~ daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of PEPCID was raised to about 5.0.[9,11]

Fasting or postprandial serum gastrin levels may be slightly elevated during periods of drug antisecretory effect,[12,13] and with chronic therapy, an increase in gastric bacterial flora may occur.[14] Gastric emptying and exocrine pancreatic function are not affected by PEPCID.[15]

9. Ryan Study No. 8
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1819

10. Ryan Study No. 7
    Item II. D. 4. Vol. 1.1, p. 88
    Item VII. F. 1. a. ii. Vol. 1.32, p. 1748

11. Smith Study No. 51
    Item II. D. 4. Vol. 1.1, p. 89
    Item VII. F. 1. a. ii. Vol. 1.33, p. 1975

12. Zinny Study No. 1
    Item II. D. 4. Vol. 1.1, p. 91
    Item VII. F. 1. a. i. Vol. 1.30, p. 1050

13. Smith Study No. 2
    Item II. D. 4. Vol. 1.1, p. 87
    Item VII. F. 1. a. ii. Vol. 1.31, p. 1518

14. Cattau Study No. 12
    Item II. D. 4. Vol. 1.1, p. 92
    Item VII. F. 1. a. iii. Vol. 1.33, p. 2101

15. Redinger Study No. 61
    Item II. D. 4. Vol. 1.1, p. 92
    Item VII. F. 1. a. iii. Vol. 1.33, p. 2036

PEPCID™
(Famotidine, MSD)

Other effects: Systemic pharmacologic effects of PEPCID in the CNS, cardiovascular, respiratory or endocrine systems have not been found to date.[16,22,23] Serum prolactin levels do not rise after intravenous bolus doses of 20 mg PEPCID[17] and no antiandrogenic effects have been detected.[18,19]

Pharmacokinetics

PEPCID is incompletely absorbed.[17,21] The bioavailability of oral doses is 40-45%.[17] Bioavailability may be slightly increased by food, or slightly decreased by antacids;[20] however, these effects are of no clinical consequence. PEPCID undergoes minimal first-pass metabolism.[21] After oral doses, peak plasma levels occur in 1-3 hours.[17,21,22] Plasma levels after multiple doses are similar to those after single doses.[22,23] Fifteen to 20% of PEPCID in plasma is protein bound.[24] PEPCID has an elimination half-life of 2.5-3.5 hours.[17,22,23] PEPCID is eliminated by renal (65-70%)[17] and metabolic (30-35%) routes.[17,21] Renal clearance is 250-450 mL/min., indicating some tubular excretion.[17,22,23]

16. Shrivastava Study No. 31
    Item II. D. 4. Vol. 1.1, p. 91
    Item VII. F. 1. a. iii. Vol. 1.33, p. 2193

17. Williams Study No. 42
    Item II. D. 3. Vol. 1.1, p. 52
    Item V. M. 12. Vol. 1.22, p. 259

18. Jensen Study No. 6
    Item II. D. 4. Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

19. Cohen Study No. 41
    Item II. D. 4. Vol. 1.1, p. 129
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4136

20. Kann Study No. 47
    Item II. D. 3. Vol. 1.1, p. 76
    Item V. M. 24. Vol. 1.25, p. 1316

21. Rotmensch Study No. 40
    Item II. D. 3. Vol. 1.1, p. 64
    Item V. M. 19. Vol. 1.23, p. 776

22. Zinny Study No. 1
    Item II. D. 3. Vol. 1.1, p. 67
    Item V. M. 20. Vol. 1.24, p. 843

23. De Schepper Study No. 748
    Item II. D. 3. Vol. 1.1, p. 54
    Item V. M. 15. Vol. 1.22, p. 388

24. Lin MSDRL Study
    Item II. D. 3. Vol. 1.1, p. 72
    Item V. M. 21. Vol. 1.24, p. 959

25. Williams Study No. 48
    Item II. D. 3. Vol. 1. 1, p. 70
    Item V. M. 25. Vol. 1.25, p. 1400

PEPCID™
(Famotidine, MSD)

Pharmacokinetics (cont'd)

Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound.[26,27] The only metabolite identified in man is the S-oxide.[28] There is a close relationship between creatinine clearance values and the elimination half-life of PEPCID.[29,30] In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min., PEPCID elimination half-lives may exceed 20 hours and adjustment of dosing intervals may be necessary[29] (see PRECAUTIONS, DOSAGE AND ADMINISTRATION). In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of PEPCID.[30]

26. Williams Study No. 42
Item II. D. 3. Vol. 1.1, p. 52
Item V. M. 12. Vol. 1.22, p. 259

27. Rotmensch Study No. 40
Item II. D. 3. Vol. 1.1, p. 64
Item V. M. 19. Vol. 1.23, p. 776

28. Yamada Yamanouchi Study
Item II. D. 3. Vol. 1.1, p. 67
Item V. M. 8 Vol. 1.22, p. 218

29. Abraham Study No. 404
Item II. D. 3. Vol. 1.1, p. 58
Item V. M. 17 Vol. 1.23, p. 639

30. Martin Study No. 744
Item II. D. 3. Vol. 1.1, p. 78
Item V. M. 16 Vol. 1.23, p. 450

PEPCID™
(Famotidine, MSD)

Clinical Studies

Duodenal Ulcer

In a U.S. multicenter, double-blind study[31] in outpatients with endoscopically confirmed duodenal ulcer, PEPCID ~~given as~~ 40 mg h.s. was compared to placebo. As shown in the table below, most patients treated with PEPCID were healed by Week 4.

Outpatients with endoscopically confirmed healed ulcers

	PEPCID 40 mg h.s. (N = 89)	Placebo h.s. (N = 97)
Week 2	*32 %	17 %
Week 4	*70 %	31 %

* statistically significantly different than placebo ($p < 0.001$)

Patients not healed by Week 4 were continued in the study. By Week 8, the incidence of healing ~~rate~~ was 83% for patients on therapy with PEPCID versus 45% for patients on placebo. The ~~rate~~ incidence of ulcer healing with PEPCID was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients on PEPCID than for patients on placebo; patients on PEPCID also took less antacid than the patients on placebo, but the difference was not clinically meaningful.

31. U.S. Multicenter Trial vs. Placebo Acute Phase
    Item II. D. 4. Vol. 1.1, p. 96
    Item VII. F. 2. a. i. Vol. 1.35, p. 2922

PEPCID™
(Famotidine, MSD)

Long-Term Maintenance Treatment of Duodenal Ulcers

The efficacy of a dosage regimen of PEPCID, 20 mg h.s. in the prevention of duodenal ulcer recurrence was compared to placebo h.s. in a U.S. double-blind, multicenter study[32] of patients with endoscopically confirmed healed duodenal ulcers. Following 6 months of therapy, PEPCID was significantly more effective ($p < 0.01$) than placebo in preventing ulcer recurrence. Of the 49 patients who completed up to 24 weeks of therapy with PEPCID 20 mg h.s., 22% of patients on PEPCID experienced ulcer recurrence, as compared to 55% of 62 patients on placebo. ~~In this clinical trial, patients have been maintained on this regimen for up to one year.~~

32. U.S. Multicenter Trial
vs. Placebo
Maintenance Phase
Item II. D. 4. Vol. 1.1, p. 108
Item VII. F. 2. a. i. Vol. 1.35, p. 2923

NDA

1962

NDA
19462

AP CTR

OCT 15 1986

NDA 19-462

Merck Sharp & Dohme Research Laboratories
Division of Merck & Co.
Attention: Gerard D. Picot, Ph.D.
West Point, PA 19486

Dear Dr. Picot:

Please refer to your June 24, 1985 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pepcid (famotidine) Tablets.

We also acknowledge receipt of your amendments dated October 3 and 7, 1986.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on October 7, 1986. Accordingly, the application is approved.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Constance Burner Henry
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

RT 10/15/86

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-100/Dr. Temple
HFN-232 (with labeling) CBHenry 10/14/86
HFN-110/CHenry/10/9/86;10/10/86;10/10/86
sb/10/10/86;10/10/86;10/14/86;10/14/86/RT
R/D: NMorgenstern/10/10/86 10/14/86
RLipicky/10/10/86;10/14/86
PDeslauriers/10/10/86 10/14/86
WBachrach/10/10/86
RWolters/10/10/86;10/14/86

APPROVAL

RT 10/14/86
10/14/86
10/14/86
Stuart Zimmerman

NDA

19462

AE LTR

SEP 30 1986

NDA 19-462

Merck Sharp and Dohme Research Laboratories
Attention: Girard Picot, Ph.D.
Division of Merck and Co., Inc.
West Point, PA 19486

Dear Dr. Picot:

Please refer to your June 24, 1985 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pepcid (famotidine) Tablets.

We also acknowledge receipt of your amendments dated August 6, September 30 (two), October 15 and 24, November 7, 13, 18 and 22; December 13, 18 and 20, 1985; January 9, 16, 14 and 16; February 14 and 24; March 4, 12 (two) and 27; April 3, 9 and 21; May 7 and 22; August 7; and September 26, 1986.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit final printed labeling for the drug. The labeling should be consistent with the content of the enclosed marked up draft and should address the following issue: The decrease in drug clearance and increased half-life with decreased renal function is well-documented. Your dosage recommendation is to adjust for this by increasing the dosing interval to 36-48 hours. It is not obvious that this is the best possible response, i.e., the one that would best match the effect of a 40 mg IV dose in normals, i.e., a dose reduction to 20 mg would also be possible. Please examine these alternatives, simulating them as necessary and reconsider the dosing recommendation. If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Division of Drug Advertising and Labeling, HFN-240
Room 16B-04
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit twelve copies of the printed labels and other labeling seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Constance Burner Henry
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Enclosure

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-240 (with draft labeling)
HFN-83
HFN-100/Dr. Temple
HFN-110/THassall/5/20/86;5/28/86;5/29/86;7/28/86
sb/5/27/86;5/28/86;7/28/86;9/25/86/3639s
R/D: RLipicky/5/30/86;7/28/86
CResnick/5/29/86
RWolters/6/9/86;7/29/86
WBachrach/6/9/86;7/30/86
NMorgunstern/6/9/86;7/30/86
GJohnson for CAR/7/29/86
VGlocklin/8/1/86
CKumkumian/8/5/86

APPROVABLE

FOR FOI PURPOSES - DELETE PARAGRAPHS 4, 5 AND 6.

NDA
19462

Chem
Rev

DIVISION OF CARDIO-RENAL DRUG PRODUCT
CHEMIST'S REVIEW #3

Date Completed: March 31, 1986

A. 1. NDA 19-462:

Sponsor: Merck Sharp and Dohme

Address: West Point, Penn 19486

AF #: 12-611

2. Product Name (s):

Proprietary- Pepcid

Nonproprietary- Famotidine

USAN- as above

Compendium- none listed

Code Name and/or number-
Refer to Chemist's Revie

3. Dosage Form and Route of Administration:
Oral tablets of 20 and 40 mg deveoped for marketing.

4. Pharmacological Category and/or Prinicpal Indications:

Potent, long-acting H_2 receptor antagonist (healer to peptic ulcers).

5. Structural Formula and Chemical Name:
See Chemist Review #1

B. 1. Initinal Submission: Receipt Date: 06-24-85
Filing Date: 08-22-85

2. Amendments:

D. Conclusions:

This application is now considered to be approvable from the standpoint of manufacturing controls. The SBA has been changed to reflect this under the "Methods Validation" section.

Stuart Zimmerman

Stuart Zimmerman, Ph.D.

4-11-86

cc:
ORIG
HFN-110
HFN-110/CSO
HFN-110/SZimmerman/4/3/86
cb/4/3/86/0871v
R/D init RWolters/4/8/86

NDA
19462

MOR

178

Medical Officer's Review
NDA 19-462, Pepcid (famotidine)

Attachments: Package insert
Reprint of paper by Howard et al

12-31-85

New Drug Application NDA 19-462
Merck Sharp & Dohme Research Laboratories
Tablets PEPCID™ (Famotidine, MSD)

Item II - Summary of Application

A. Annotated Package Circular

HFN-110/C50

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA 19-462

Name of Drug: Pepcid (famotidine)

Sponsor: Merck Sharp & Dohme Research Laboratories

Formulation: Tablets 20 mg and 40 mg.

Route of Administration: Oral

Proposed Clinical Use: Treatment of peptic ulcer disease.

Pharmacological Class: H_2-blocker.

Date of Submission: June 24, 1985

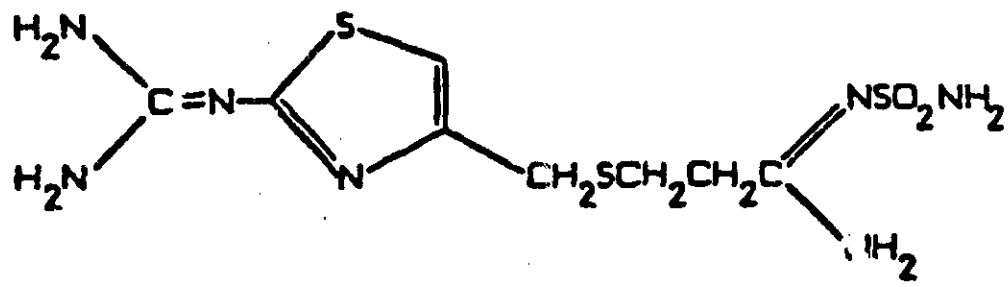
Material Submitted for Clinical Review:

Volume 1.1:	Summary of clinical reports
Volumes 1.27-1.38:	Full clinical reports
Volumes 1.49-1.53:	Case report forms on microfiche

Date Review Completed: 6 December 1985.

Reviewer: William H. Bachrach, M.D.

I. Background/Rationale: Famotidine, 3-[[[2-[(amino-iminomethyl) amino] 4-thiazolyl] methyl] thio]-M-(aminosulfonyl)-propanimidamide, with the following structural formula



HFN-110/CSO

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA 19-462

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Sponsor: Merck Sharp & Dohme Research Laboratories

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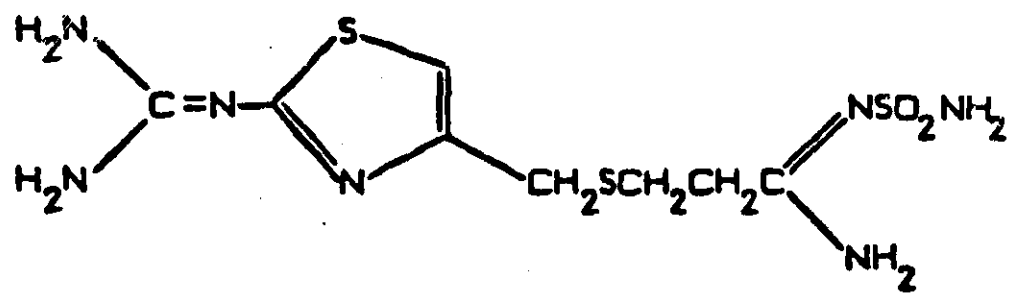


is a long-acting H_2-blocker developed by Yamanouchi Pharmaceutical Company, Ltd., and licensed to Merck & Company, Inc. for distribution outside of Japan.

H_2-blockers inhibit gastric acid secretion and, primarily by this action, accelerate healing of peptic ulcers. Two H_2-blockers have been approved for marketing in the U.S., the first cimetidine, the second ranitidine. The use of H_2-blockers in patients with peptic ulcer disease has resulted in decreased patient morbidity and, according to some reports, in the need for elective operations, but the incidence of surgery for complications has not diminished.

Famotidine has been shown in animal and human studies to inhibit basal and stimulated gastric acid secretion. Based on these data, doses of famotidine have been selected for the evaluation of its effectiveness and safety in patients with peptic ulcer disease. Because of its long duration of action, it is expected that a once-a-day bedtime regimen will be effective.

No marketing experience is available because famotidine had not been marketed in any country at the time of submission of this NDA.

II. Clinical Pharmacology

A. Human tolerance

1. Japanese study

a. Title: An open study to assess safety, tolerability and drug levels in blood and urine of famotidine administered orally to normal male volunteers.

b. Investigators: T. Miwa, M.D. and M. Miwa, M.D., School of Medicine, Tokai University.

c. Design of study: doses of 5, 10, 20, 40, 80 and 160 mg were administered orally to each of 2 volunteers after the results of the preceding dose had been reviewed; 20 and 40 mg b.i.d. for 5 days were administered to 3 of the subjects after satisfactory completion of the single-dose sequence. The drug was administered on an empty stomach in the single-dose studies and 1/2 hour after meals in the repetitive dose study.

d. Results

(1) Safety: in none of the 12 volunteers were there any changes attributable to the drug in the vital signs, ECG, hemogram (including Coombs test), blood chemistry or urinalysis.

(2) Plasma concentration (figure 1): plasma levels, measurable with all except the 5 mg dose, were proportional to the size of the dose. Peak levels were reached between 2 and 3 hours. Drug levels were still detectible at 12 hours after doses of 40 mg and greater, but not at 24 hours at any of the single doses. No plasma accumulation of the drug was apparent in the multiple-dose studies.

(3) Urinary excretion (figure 2): the cumulative excretion of the drug amounted to 30-40% for all doses; most of the drug was excreted within the first 8 hours. After multiple dose administration, the daily excretion remained constant.

Figure 1
Bioavailability of Single Oral Doses

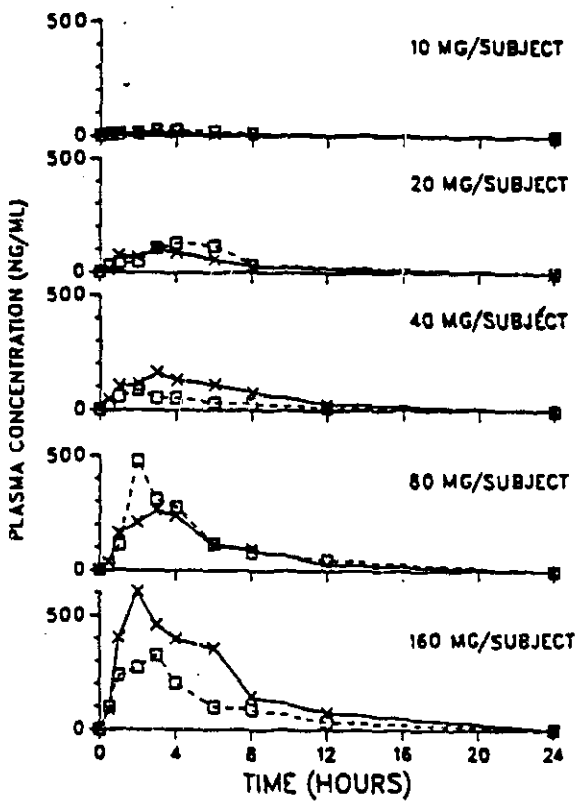
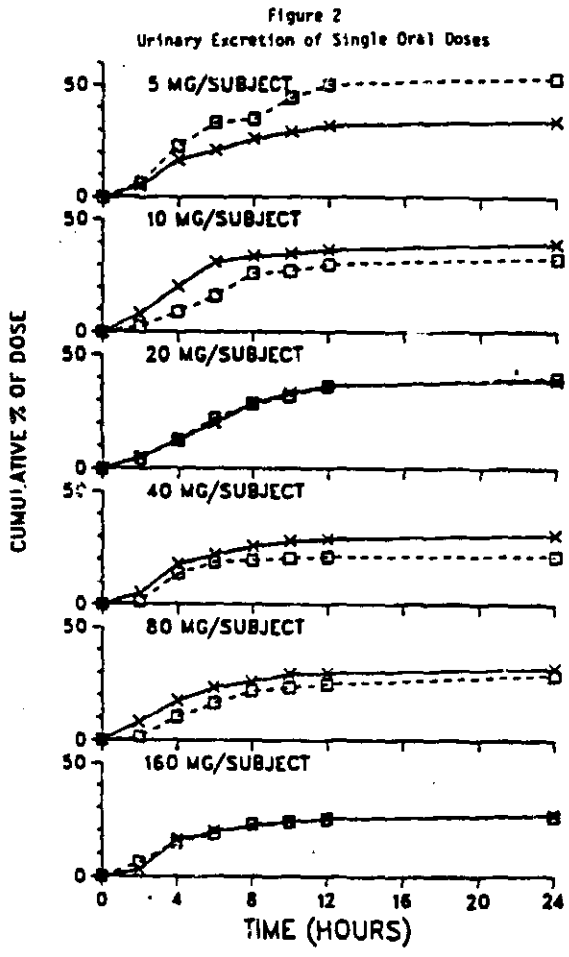


Figure 2
Urinary Excretion of Single Oral Doses



e. Conclusions: famotidine was well tolerated by healthy male volunteers when administered in single oral doses of 5 to 160 mg and in multiple 20 and 40 mg b.i.d. oral doses for 5 days. The drug was rapidly absorbed with peak levels at 2-3 hours proportional to the size of administered doses. Thirty to 40% of the drug was excreted in the urine; no accumulation was observed. No adverse effects were reported.

2. Study No. 1

a. Title: A double-blind, single, rising dose, placebo-controlled study to determine safety, tolerability and dose proportionality of blood and urine levels of famotidine administered orally to healthy volunteers.

b. Investigators: Miguel A. Zinny, M.D., Medical and Technical Research Associates, Needham, MA and Norman D. Grace, M.D., Tufts University School of Medicine, Boston.

c. Design of study: in this placebo-controlled study in 15 healthy volunteers, the subjects were admitted to the Clinical Research Unit the evening preceding each treatment period and remained confined to the unit until completion of the 48-hour treatment period. Following an overnight fast, the subjects received a single oral dose of famotidine 5, 10, 20 or 40 mg with a placebo control interspersed randomly in one of the treatment periods. Study periods were separated by intervals of one week. Vital signs were measured at 0, 2, 4, 8, 12, and 24 hours post-dosing. Laboratory safety parameters, including ECGs, were assessed before and after 24 hours of treatment at each study period. Plasma and urine samples collected at appropriate intervals were frozen for analysis at the sponsor's laboratories. At appropriate intervals post-treatment the subjects were asked about any unusual symptoms. In this and many of the following studies, symptoms were graded:

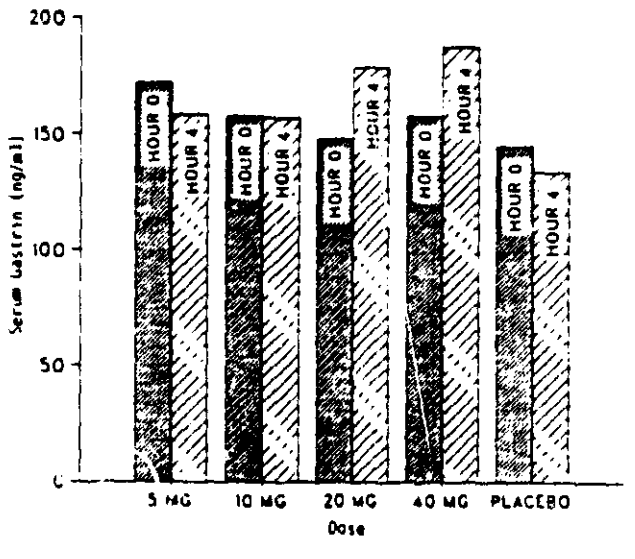
None:	no awareness of abnormal signs or symptoms
Mild:	aware of symptoms, but easily tolerated
Moderate:	discomfort enough to interfere with but not prevent daily activity
Severe:	unable to perform usual daily activities

d. Results

(1) Safety parameters: no abnormalities of vital signs, hemogram, serum electrolytes or urinalysis were observed with either famotidine or placebo. One of the subjects experienced transient lightheadedness after placebo. There were no other clinical adverse events.

(2) Serum gastrin (figure 3): mean serum gastrin levels at 0 hour were higher for all doses of famotidine than placebo. Four hours after treatment, mean gastrin levels were statistically significantly higher after the 20 and 40 mg doses than after the lower doses and placebo.

Figure 3
Mean Serum Gastrin 0-4 Hours Post-Dose (N=15)



(3) The results of serum prolactin determinations are described below under IID, "Hormonal effects."

e. Conclusions: famotidine is well-tolerated in single oral doses up to 40 mg. Doses of 20 mg and 40 mg increase serum gastrin.

3. Study No. 748

a. Title: A double-blind, placebo-controlled study to investigate the safety and tolerability of repeated doses of famotidine in healthy subjects.

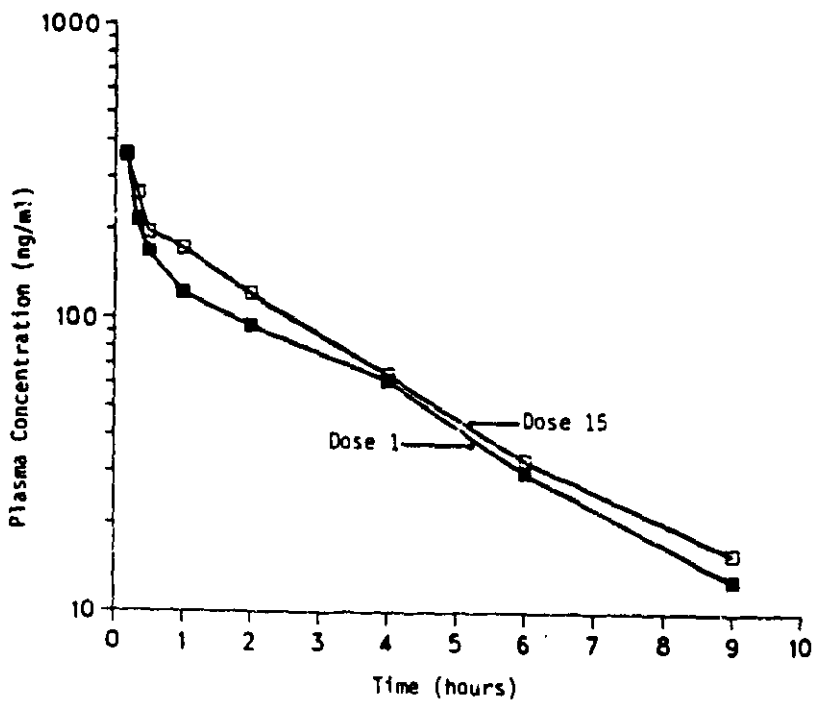
b. Investigator: Professor P. J. DeSchepper, Department of Pharmacology, Campus Gasthuisberg, Leuven, Belgium.

c. Design of study: at 0800 and 1700 hours for 7.5 days, the subjects received intravenous bolus injections of 5 ml containing either famotidine 20 mg (6 subjects) or placebo (2 subjects). Doses on odd-numbered days were administered in the left arm and on even numbered days in the right arm. Tolerability and safety were assessed by monitoring pain and induration at the injection site, ECG, vital signs, clinical chemistry, urinalysis, clinical adverse experiences and any changes in physical status. Plasma levels and urinary excretion of famotidine were determined after the first and 15th doses.

d. Results

(1) Plasma levels of famotidine (figure 4): the plasma is cleared rapidly of the administered drug with no evidence of a cumulative delay in clearance.

Figure 4
Mean Plasma Concentration of Famotidine
Following Single and Repeated I.V. Doses (N = 6)



(2) Safety: induration and local hyperemia occurred in 2 of the 6 famotidine treated subjects; in one of these, the investigator attributed the result to a slight extravasation of the drug during the last 15 seconds of the injection. Epigastric discomfort was reported by 3 famotidine and 1 placebo-treated subjects. A few laboratory safety parameters showed a statistically significant change after administration of both famotidine and placebo. No consistent changes were observed in physical examination or ECGs. A statistically significant decrease in systolic blood pressure was noted in subjects receiving placebo as well as in those receiving famotidine. Thus, clinical adverse experiences were few and they were similar for drug- and placebo-treated subjects.

e. Conclusions: famotidine 20 mg b.i.d. intravenously for 15 doses was well-tolerated in healthy subjects.

4. Summary of tolerance studies: In 3 studies in a total of 36 healthy volunteers famotidine was well tolerated in single oral doses up to 160 mg, in repetitive oral doses of 20 mg and 40 mg b.i.d. for 5 days, and in intravenous doses of 20 mg b.i.d. for 7.5 days. The only observation of possible clinical significance was a mild elevation of serum gastrin levels after oral administration of 20 and 40 mg. Additional tolerance data are derived from studies not designed primarily for this purpose.

B. Bioavailability/Pharmacokinetics

1. Study No. 748: the protocol has just been reviewed above under "Human Tolerance." The pharmacokinetic data derived from that study show (table 1) that after repeated administration of 20 mg twice daily for 15 doses, the drug was cleared primarily through the kidney and that the half-life was a little less than 3 hours.

TABLE 1

Pharmacokinetic parameters (geometric mean) of famotidine following repeat intravenous administration of 20 mg BID daily for 15 doses in 6 healthy subjects.

Plasma Clearance ml/min	313
Renal Clearance, ml/min	259
Non-renal Clearance*, ml/min	54
Half-life, hours	2.7
Urinary Recovery, % of Dose	82.9

*Difference between plasma clearance and renal clearance.

2. Study No. 42

a. Title: An open, 4-way cross-over, single dose, comparative bioavailability study of famotidine capsules 20 mg, tablets 20 mg and 40 mg, and intravenous injection of 20 mg.

b. Investigator: Roger L. Williams, M.D., University of California, San Francisco, CA.

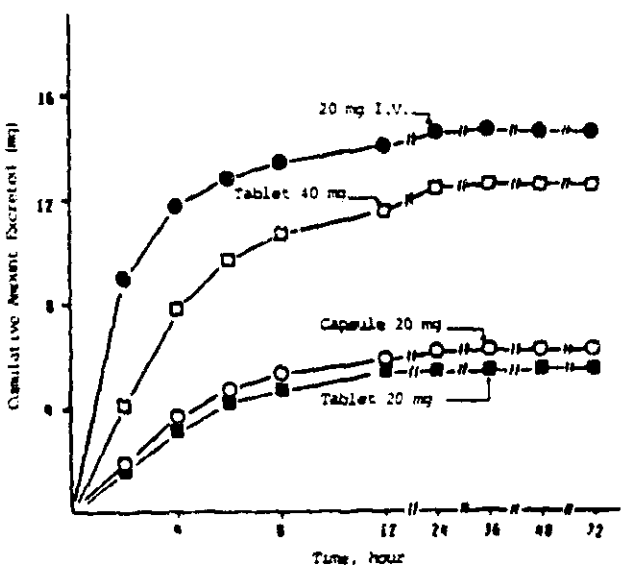
c. Design of study: this was an open, single-dose, 4-way cross-over study in 16 healthy volunteers assigned randomly to receive each of the 4 treatments listed in the title with a 1-week washout between treatments. Following administration of the test medications, plasma and urine samples were taken at appropriate intervals and were assayed for levels of famotidine.

d. Results

(1) Safety: no clinical or biochemical adverse experiences were reported at any time during the study.

(2) Pharmacokinetics: the time to maximum blood levels was the same for all 3 oral doses but reached a significantly higher level and remained higher for a longer period time with the 40 mg tablet. Approximately 30% of the drug was excreted in the urine over a 72 hour period after all 3 oral doses (figure 5), which was about half of the amount excreted after the intravenous dose. The total body clearance averaged approximately 28 l/h and the mean half-life was around 3 hours. For all practical purposes the 3 oral formulations had a similar bioavailability, approximating 45%.

Figure 5
Cumulative Amount of Famotidine Excreted in the Urine



e. Conclusions: single oral doses of famotidine, capsules 20 mg, tablets 20 mg or 40 mg, and IV dose of 20 mg, were well-tolerated. Systemic bioavailability approximated 45% and was similar for all 3 oral doses. The 20 mg capsule and 20 mg tablet are bioequivalent.

3. Study No. 556

a. Title: A two-part, open study in healthy elderly subjects to examine the pharmacokinetic profiles of famotidine when administered as a single intravenous and single oral dose (Part I) and repeated oral doses (Part II).

b. Investigator: B. Martin, M.D., Bios Consulting and Contract Research, Ltd., Surrey, England.

c. Design of study: open, two-part study in 8 healthy elderly subjects with random cross-over treatment sequence. During the first part of the study, fasting subjects received either a single intravenous dose of 20 mg or an oral dose of 40 mg. In the second part of the study they received 40 mg b.i.d. for 9 doses. Plasma and urine samples were collected according to the same schedule as that in the study reviewed above. Safety parameters were assessed by both clinical observation and conventional laboratory tests.

d. Results

(1) Safety: no drug-related adverse events were reported.

(2) Pharmacokinetics: plasma concentration of famotidine following the administration of a single oral dose or following the last of the multiple oral doses of 40 mg were similar (figure 6) as were the curves for urinary secretion of famotidine (figure 7). The disposition of the drug was therefore similar to that found in the younger volunteers reported in the study reviewed above. The bioavailability in these elderly subjects was 40%, i.e., in the same range as that in the younger subjects.

Figure 6
Plasma Concentration of Famotidine in Healthy Elderly (N=8)

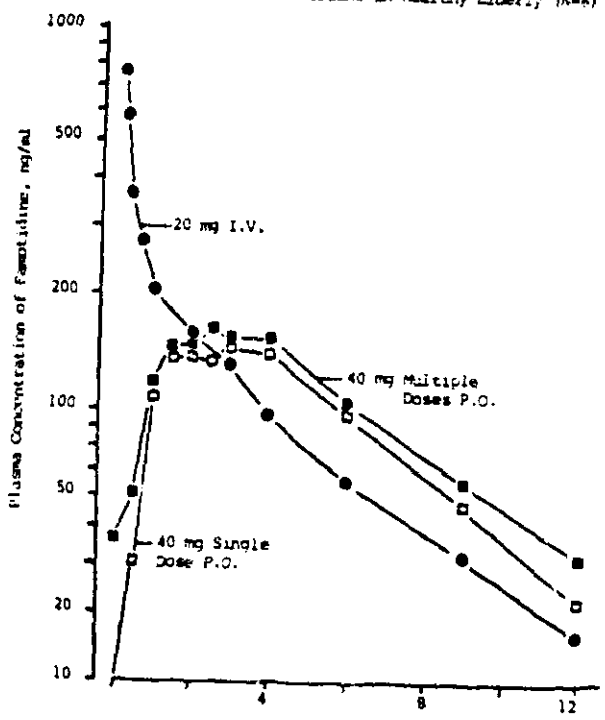
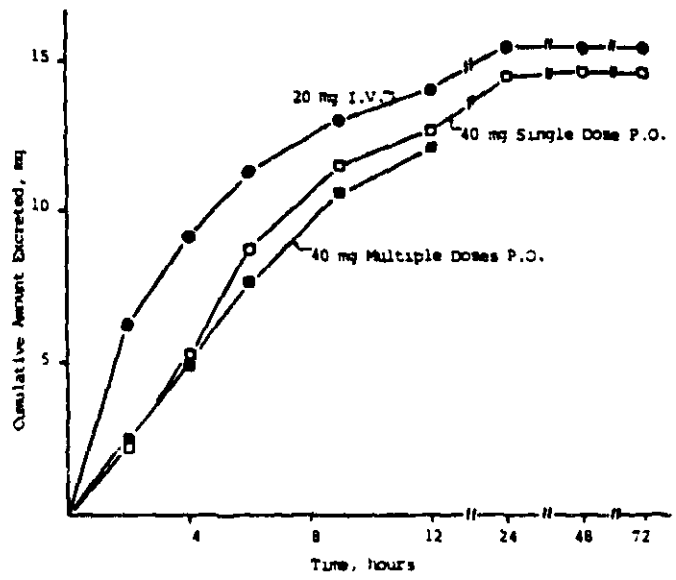


Figure 7
Cumulative Urinary Excretion of Famotidine in Healthy Elderly (N = 8)



e. Conclusions: the results of this study indicate that famotidine is as safe and as bioavailable in healthy elderly subjects as in the younger age group.

4. Study No. 527

a. Title: An open study to assess the disposition kinetics and safety of famotidine in patients with moderate to severe renal insufficiency.

b. Investigators: Paul Abraham, M.D. and William F. Keane, M.D., Drug Evaluation Unit, Regional Kidney Disease Program, Hennepin County Medical Center, Minneapolis, MN.

c. Design of study: 18 patients with moderate to severe renal insufficiency were assigned to one of three groups according to the degree of renal impairment. Group 1 (7 subjects) had a creatinine clearance of 30-50 ml/min and a serum creatinine greater than 3 mg %; the creatinine clearance in Group 2 (5 subjects) was 10-30 ml/min, in Group 3 (6 subjects) less than 10 ml/min. Patients in Group 3 were anuric; hemodialysis was disconnected one day prior to the administration of famotidine. On the study day a

single intravenous injection of famotidine 10 mg was given over a 1 minute period. Plasma and urine samples were collected according to essentially the same schedule as in the protocols reviewed above. Insulin and creatinine clearances were determined for 30 minute periods 1.5 hours before and 4 hours after administration of the drug. The patients were observed for any adverse clinical reactions; conventional laboratory tests were performed before and after drug administration.

d. Results

(1) Safety: no clinically important drug-related adverse events occurred during this study.

(2) Pharmacokinetics: in patients with impairment of renal function plasma clearance (figure 8) and renal clearance (figure 9) of the drug are diminished pari passu with the degree of renal impairment. The total area under the curve (figure 10) and the half-life (figure 11) are inversely proportional to the creatinine clearance. The non-renal clearance was not affected by the degree of impairment of renal function. Considering that the upper limit of half-life in healthy young and healthy elderly subjects was in the neighborhood of 5 hours, it is apparent that the half-life of famotidine becomes prolonged with a degree of renal impairment characterized by a creatinine clearance of less than 30 ml/min.

Figure 8
Renal Function and Plasma Clearance in Renal Impaired Patients

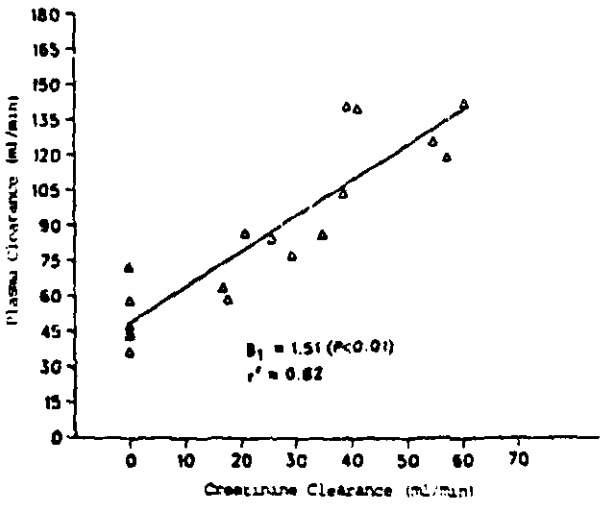


Figure 9
Renal Function and Renal Clearance in Renal Impaired Patients

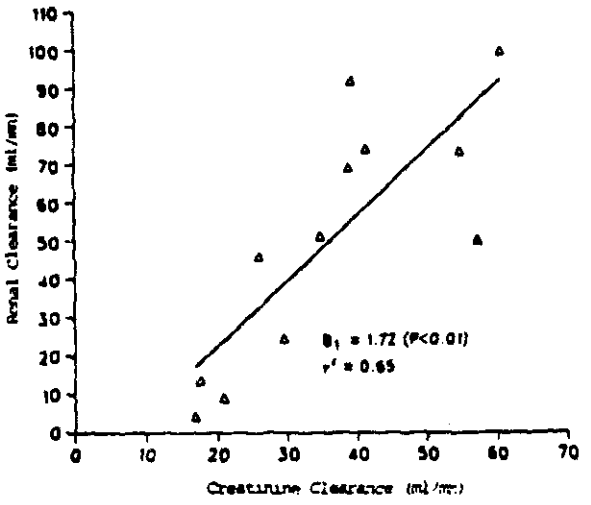


Figure 10
Renal Function and Total Area Under the Curve in Renal Impaired Patients

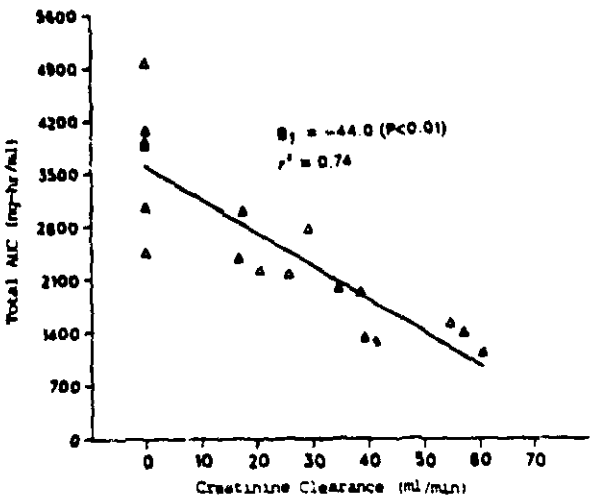
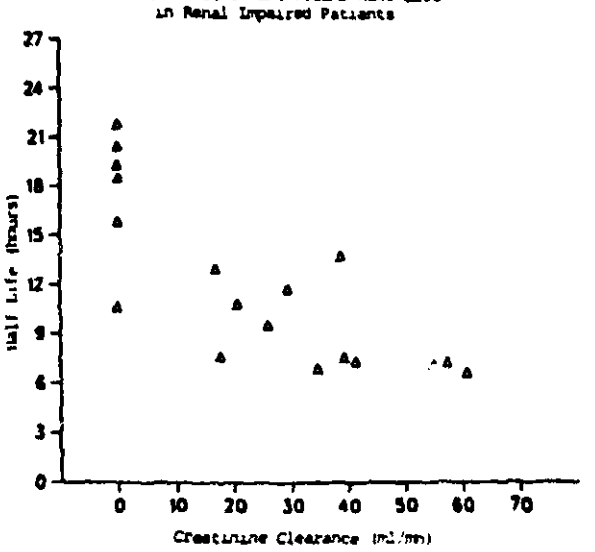


Figure 11
Renal Function and Plasma Half Life in Renal Impaired Patients

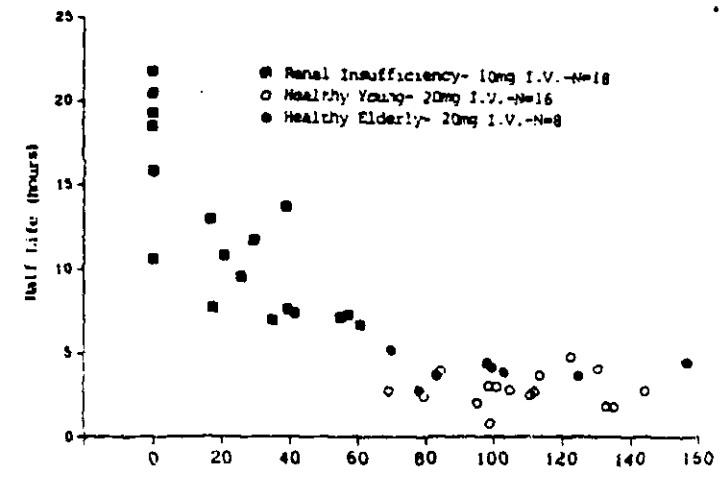


Note: Since the relationship between plasma elimination half-life and renal function is known to be non-linear, simple linear regression analysis was not performed.

e. Conclusion: the results of all parameters of disposition of famotidine in patients with decreased renal function indicate that in patients with creatinine clearance of less than 30 ml/min the dosage of famotidine must be adjusted downward to achieve blood levels comparable with those obtainable at any given dose in patients with normal renal function or with lesser degrees of renal impairment.

5. Summary of bioavailability/pharmacokinetic studies: the results of 4 studies evaluating famotidine in single intravenous doses of 10 mg and 20 mg, single oral doses of 10 mg, 20 mg and 40 mg, and multiple oral doses of 40 mg indicate that the drug is 40-45% bioavailable, has a mean half-life of about 3 hours and is cleared from the body primarily via the kidneys. The pharmacokinetics are approximately the same in elderly as in younger subjects, while in patients with renal insufficiency significant delay in excretion of the drug appears when the degree of renal impairment amounts to a creatinine clearance of less than 30 ml/min. A reduction in the famotidine dose would therefore be indicated in such patients. The comparative half-lives of famotidine in the healthy young, the healthy elderly and the renally-impaired subjects are shown graphically in figure 12. No drug-related adverse effects were documented in any of these studies.

Figure 12
Relationship of Famotidine Half Life to Creatinine Clearance



C. Gastric and pancreatic function

1. Pentagastrin-stimulated gastric secretion

a. Study No. 725

(1) Title of study: Comparison of 3 different doses of famotidine on pentagastrin-stimulated gastric acid secretion.

(2) Investigator: Professor Richard H. Hunt, McMaster University Medical Centre, Hamilton, Canada.

(3) Design of study: double-blind, four-way, placebo-controlled, cross-over study in which 8 healthy volunteers were assigned randomly to receive 3 dosage regimens of famotidine intravenously to achieve plasma concentrations of 10, 30 and 90 ng/ml respectively, or placebo. In the morning after an overnight fast the subjects were intubated with a 14 French double-lumen tube, the contents of the stomach emptied, and continuous aspiration carried out for 7 consecutive hours. The first hour assessed basal acid secretion. A 19-gauge butterfly needle was then inserted into a vein in each forearm to provide for administration of pentagastrin and test drugs separately. A loading dose of famotidine was administered as a bolus injection over 2 minutes and constant infusion started immediately thereafter at a rate to provide the desired blood level. The amounts of famotidine administered were:

e. Conclusion: the results of all parameters of disposition of famotidine in patients with decreased renal function indicate that in patients with creatinine clearance of less than 30 ml/min the dosage of famotidine must be adjusted downward to achieve blood levels comparable with those obtainable at any given dose in patients with normal renal function or with lesser degrees of renal impairment.

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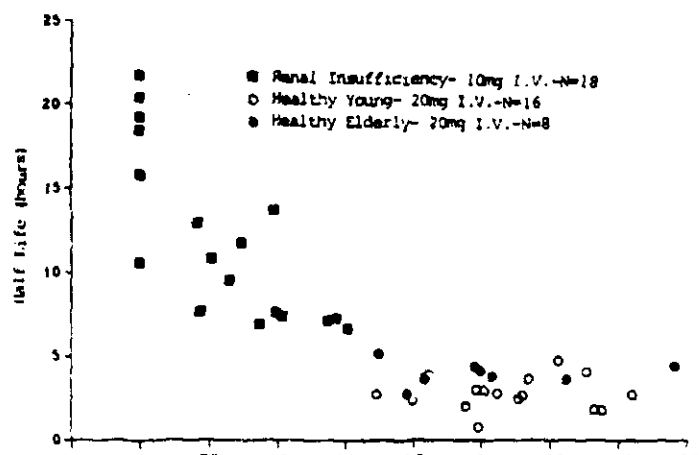

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(1) Title of study: Comparison of 3 different doses of famotidine on pentagastrin-stimulated gastric acid secretion.

(2) Investigator: Professor Richard H. Hunt, McMaster University Medical Centre, Hamilton, Canada.

(3) Design of study: double-blind, four-way, placebo-controlled, cross-over study in which 8 healthy volunteers were assigned randomly to receive 3 dosage regimens of famotidine intravenously to achieve plasma concentrations of 10, 30 and 90 ng/ml respectively, or placebo. In the morning after an overnight fast the subjects were intubated with a 14 French double-lumen tube, the contents of the stomach emptied, and continuous aspiration carried out for 7 consecutive hours. The first hour assessed basal acid secretion. A 19-gauge butterfly needle was then inserted into a vein in each forearm to provide for administration of pentagastrin and test drugs separately. A loading dose of famotidine was administered as a bolus injection over 2 minutes and constant infusion started immediately thereafter at a rate to provide the desired blood level. The amounts of famotidine administered were:

Plasma concentrations ng/ml	Loading dose (2 min) mcg/kg	Rate of infusion mcg/kg/hr
10	3	4.3
30	9	12.9
90	27	38.7

The placebo arm consisted of saline infused at a rate of 50 ml/h. At the end of the first 2 hours pentagastrin infusions were administered in 5 incremental infusion rates, each for a period of 1 hour, starting with 0.1 mcg/kg/h and ending with 2.0 mcg/kg/h. Blood samples for assay for famotidine were obtained at baseline and at hourly intervals for 7 hours. The volume of gastric secretion was measured every 10 minutes and analyzed for pH, titratable acidity and pepsin concentration. The first 30 minutes of each hour was considered a stabilizing stage; the collections of the last three 10-minute intervals of each hour were averaged and doubled to obtain the hourly rates of secretion. Observations to assess safety included a hemogram, clinical chemistry and urinalysis.

(4) Results

(a) Safety: no drug-related adverse events occurred during these studies.

(b) Gastric secretion: 8 volunteers completed the studies. During pentagastrin stimulation, famotidine significantly reduced gastric acid output in a dose-related fashion, reaching almost 100% inhibition with the highest plasma concentration of the drug (figure 13), an effect resulting from reduction in both the volume (figure 14) and the concentration (figure 15) of acid. Paradoxically, a sustained elevation of pH was observed with only the dose which yielded a blood level of 90 ng/ml (figure 16). Pepsin concentration was not significantly different with the 3 doses than with placebo, but as a result of the great reduction in volume the pepsin output was correspondingly reduced.

Figure 13
Mean Acid Output For Each Ten-Minute Collection (N=8)

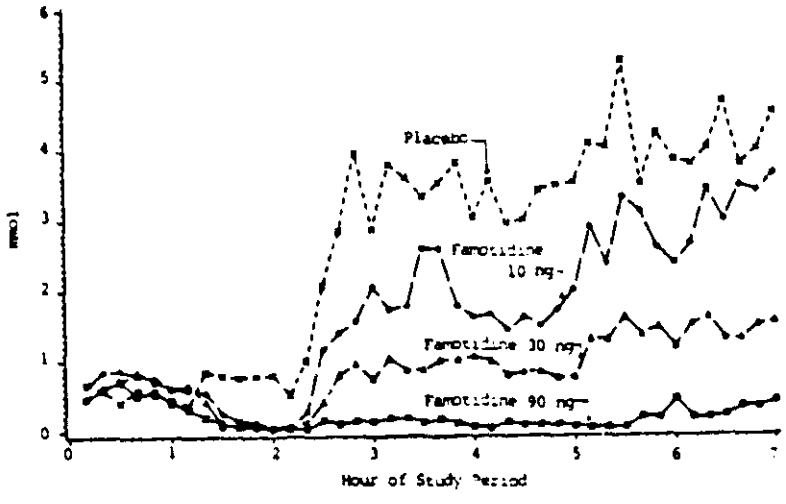


Figure 14
Mean Volume For Each Ten-Minute Collection (N=8)

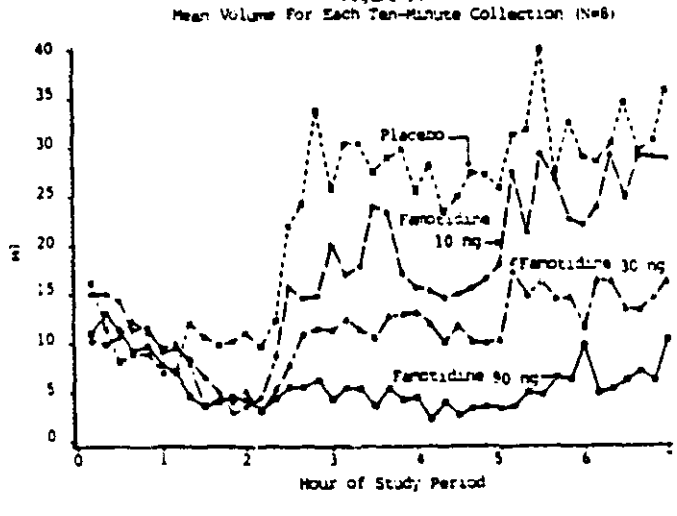


Figure 15
Mean Acid Concentration For Each Ten-Minute Collection (N=8)

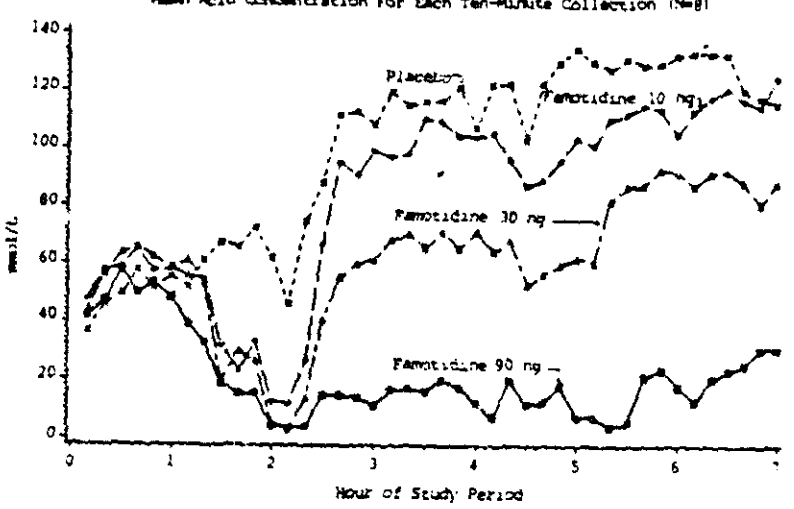
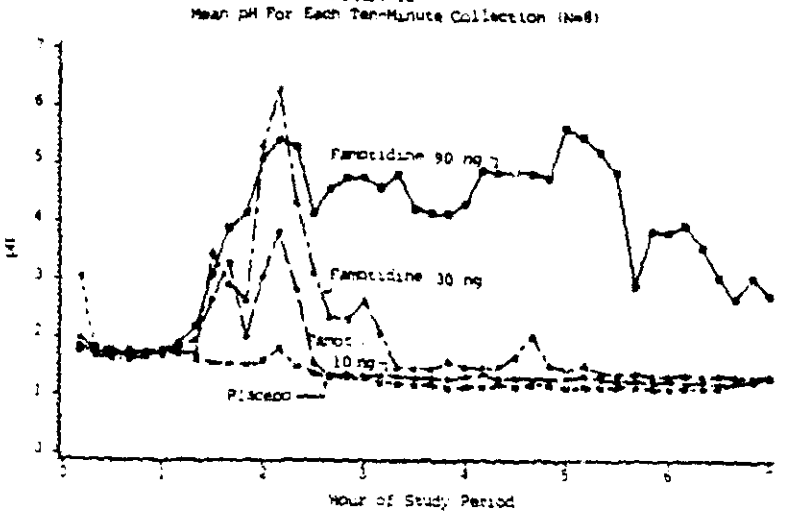


Figure 16
Mean pH For Each Ten-Minute Collection (N=8)



(5) Conclusions: constant intravenous infusions of famotidine at rates estimated to produce plasma concentrations of 10, 30, and 90 ng/ml inhibited basal gastric secretion maximally and pentagastrin-stimulated secretion in a concentration-dependent manner. At a concentration of 90 ng/ml acid secretion is almost completely inhibited. The sponsor concludes that for maximal therapeutic antisecretory effects, this level of plasma concentration might be desirable.

(6) Comment: the investigator must have had some basis for knowing a priori what rates of infusion would produce the desired blood levels. It will be interesting to hear from the sponsor how it was done.

b. Study No. 2

(1) Title: A double-blind, placebo and active controlled study to determine the effect of three separate incremental oral doses of famotidine on pentagastrin-stimulated gastric acid secretion in healthy volunteers.

(2) Investigator: J. Lacey Smith, M.D., Baylor College of Medicine, Houston, TX.

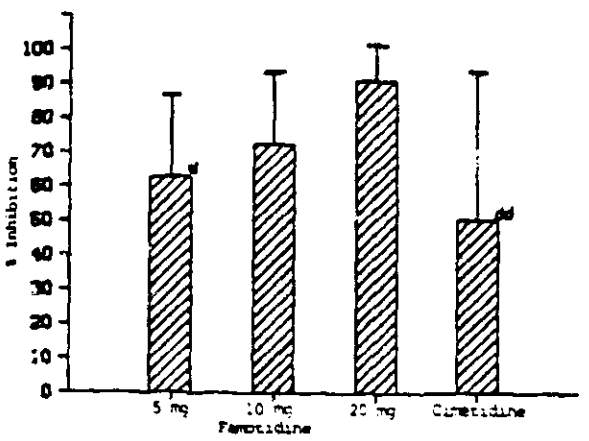
(3) Design of Study: double-blind, cross-over, placebo and active drug (cimetidine) controlled study. Ten healthy volunteers eligible for the study on the basis of medical history, physical examination, laboratory tests and ECGs received single doses of famotidine 5, 10, and 20 mg placebo, or cimetidine 300 mg all administered orally with water 200 ml. The subjects remained ambulatory for 1 1/4 hours and were then intubated with a 16 French double-lumen tube. Volume of secretions lost through the pylorus was corrected by infusion of a standard solution of phenol-red. Gastric aspirates were collected for three 15-minute intervals followed by IM injection of pentagastrin 6 ug/kg, followed by 15-minute collections of the continuously aspirated secretions for one hour. An additional investigation enlisted 6 of the volunteers who were found to be high basal acid secretors (more than 2.0 mEq/h) and/or brisk responders to pentagastrin (more than 20 mEq/h) in a study to assess the effect of famotidine 20 mg administered orally at 8 p.m. on the gastric secretory response to a single IM dose of pentagastrin given 10 and 12 hours later.

(4) Results

(a) Safety: no adverse events occurred during this study.

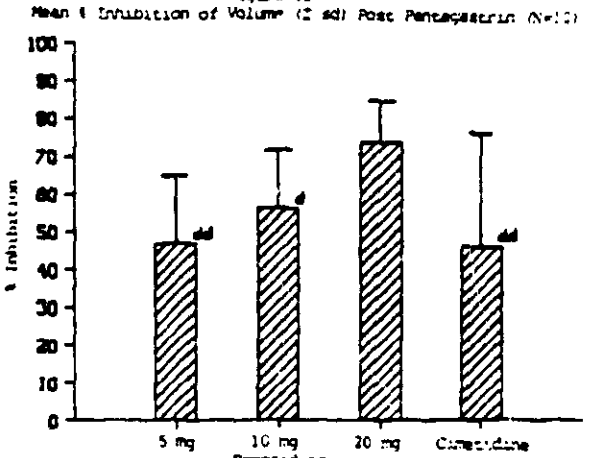
(b) Gastric secretion: pentagastrin-stimulated acid output was inhibited by famotidine in a dose-related fashion (figure 17), a result primarily of inhibition of volume of secretion (figure 18). The percent inhibition with cimetidine 300 mg was of the same order as that with famotidine 5 mg. Basal gastric secretion was decreased by all active treatments in comparison with placebo. Among the 6 subjects in the additional study, inhibition of pentagastrin-stimulated acid secretion 10-12 hours following famotidine 20 mg ranged from 18% to 88% with a mean of 53.6%.

Figure 17
Mean % Inhibition of Acid (± sd) Post Pentagastrin (N=10)



d, dd significantly different than famotidine 20 mg, p<0.05, p<0.01 respectively

Figure 18
Mean % Inhibition of Volume (± sd) Post Pentagastrin (N=10)



d,dd significantly different than famotidine 20 mg, p<0.05, p<0.01 respectively

(5) Conclusion: Famotidine administered orally approximately one hour before intramuscular injection of pentagastrin inhibited the gastric secretion in the following hour significantly more than did placebo with all doses tested. The inhibitory effect of famotidine 5 mg was comparable to that of cimetidine 300 mg. Famotidine 20 mg diminished the secretory response in varying degrees to an injection of pentagastrin given up to 11 hours later.

c. Study No. 3

(1) Title of Study: A double-blind placebo and active drug-controlled study to determine the effect of three separate incremental oral doses of famotidine on pentagastrin-stimulated gastric acid secretion in healthy volunteers.

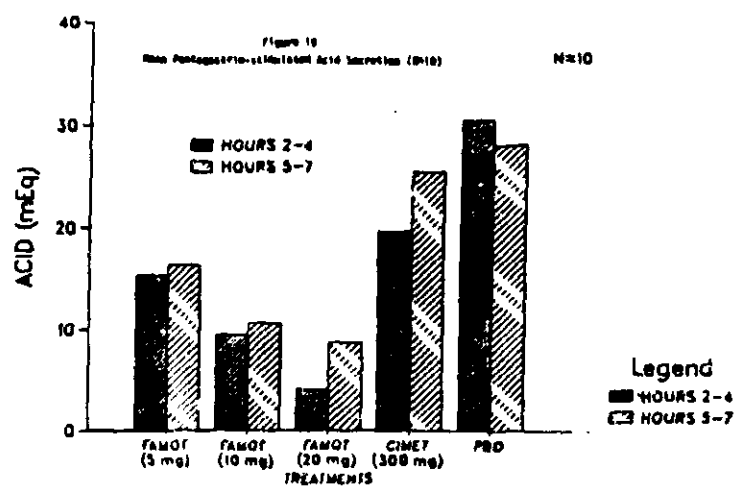
(2) Investigator: Richard W. McCallum, M.D., Yale University School of Medicine, New Haven, CT.

(3) Design of Study: double-blind, cross-over, placebo and active drug study in a 10 healthy volunteers. The procedure was similar to that of study No. 2 except that pentagastrin was infused intravenously at a rate of 1 mcg/kg/hr for two hours starting two hours after oral administration of famotidine 5, 10 or 20 mg, or cimetidine 300 mg or placebo. At the conclusion of the infusion, the subjects were permitted to become ambulatory for one hour after which a second continuous two-hour pentagastrin infusion was started. At the completion of this infusion, which was seven hours after administration of the test substance, the study day was completed.

(4) Results

(a) Safety: no drug-related adverse events were reported.

(b) Gastric secretion: a dose-related reduction in acid output following famotidine was observed after both pentagastrin-stimulated periods (figure 19). During the first period of stimulation acid output with famotidine 5, 10 and 20 mg was reduced 50%, 69% and 87% respectively, compared to 36% for cimetidine. During the second period of stimulation the respective degrees of inhibition were 41%, 62%, 69% and 7%.



(5) Conclusion: the results confirm those of the previous study in showing that famotidine inhibits pentagastrin-stimulated gastric acid output in a dose-related fashion for at least 7 hours after oral administration of the drug. In this study, moreover, the degree of inhibition with famotidine 5 mg was both greater and more prolonged than with cimetidine 300 mg.

d. Study No. 5

(1) Title: A double-blind, placebo controlled study to determine the effect of three separate incremental oral doses of famotidine on nocturnal and pentagastrin-stimulated gastric acid secretion in healthy volunteers.

(2) Investigator: Sidney Cohen, M.D., and Ann Ouyang, M.D., Hospital of the University of Pennsylvania, Philadelphia, PA.

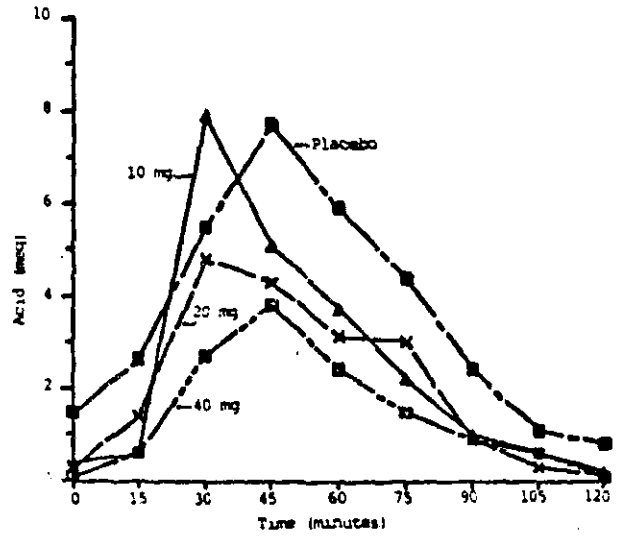
(3) Design of Study: the effects of single oral doses of famotidine 10, 20 and 40 mg were compared to placebo on pentagastrin-stimulated gastric acid secretion 9 1/2 hours after administration of the drug in 8 healthy volunteers in a double-blind, four-period cross-over study with a washout interval of 72 hours separating the treatments. The medication or placebo was self-administered at midnight. Pentagastrin 6 ug/kg was given subcutaneously 9 1/2 hours after ingestion of the drug; gastric secretion was determined for two hours thereafter.

(4) Results

(a) Safety: the only adverse experiences were those attributable to administration of pentagastrin.

(b) Gastric secretion (figure 20): during the first hour of pentagastrin stimulation there were statistically significant reductions of gastric acid output with famotidine 20 mg and 40 mg compared to placebo; during the second hour significant reduction of acid output occurred with all 3 doses of famotidine.

Figure 20
Mean Pentagastrin Stimulated Acid Secretion



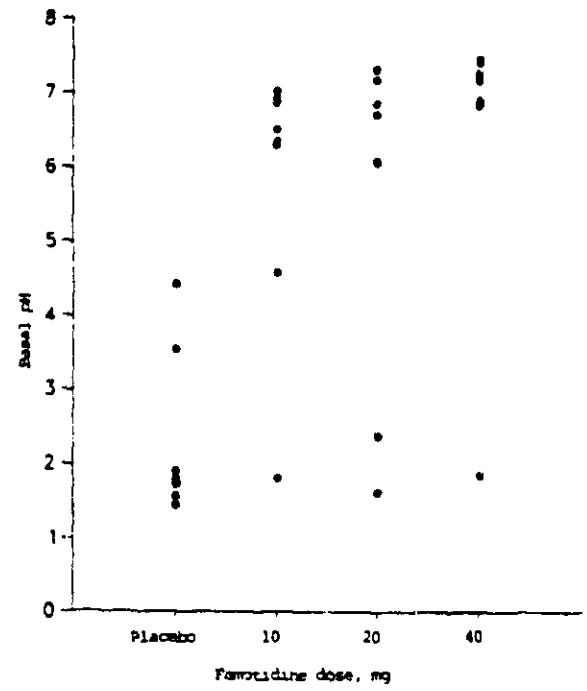
(5) Conclusion: Famotidine in single oral doses of 10, 20 and 40 mg inhibits pentagastrin stimulated volume and acidity of gastric secretion in a dose-related manner for a period of more than 11 hours.

e. Summary of studies on pentagastrin-stimulated secretion: famotidine in the proposed daily therapeutic doses (40 mg h.s. for short-term treatment of peptic ulcer, 20 mg h.s. for prevention of recurrence) inhibits acid secretion stimulated by pentagastrin administered by continuous IV, intramuscular or subcutaneous injection. The inhibition amounts to 60-70% compared to placebo, and lasts for up to 12 hours in some cases. A single oral dose of 5 mg has approximately the same inhibitory effect as a dose of 300 mg of cimetidine.

2. Nocturnal secretion

a. Study No. 5: the protocol was as reviewed above under IIC1d. The pH of nocturnal gastric secretion was elevated (figure 21) by single oral doses of famotidine 10, 20 and 40 mg for at least 8 hours. The pH values were above 6 in only 1 of the 8 subjects on placebo contrasted with 5 on famotidine. With the 40 mg dose the pH in all 8 subjects was above 7.0.

Figure 21
pH Eight Hours After Drug (N=8)



b. Study No. 7

(1) Title: A double-blind, placebo-controlled study to determine the effects of four oral dose levels of famotidine at the beginning and end of a 5-day dosing regimen on nocturnal and food stimulated acid secretion in volunteers who are hyper-secretors.

(2) Investigator: Jerome Ryan, M.D., Clinical Research Center, Inc., New Orleans, LA.

(3) Design of Study: the study was divided into three parts:

Part I evaluated nocturnal and food-stimulated acid secretion on the first and fifth day when doses of famotidine 5, 10, 20 and 40 mg and placebo were administered to 4 healthy volunteers at 9:00 PM each evening for 5 days. Each treatment period was separated by a 5 day interval. The study was discontinued when it became apparent that an effective dose had not been identified with the dosage regimens evaluated. Other dosage regimens were then explored in an open-label pilot study.

Part II evaluated the effects on nocturnal and meal-stimulated acid secretion over a 22-hour interval after administration of famotidine 40 or 80 mg or placebo at 7:00 AM in an open-label design to 2 healthy volunteers. Each treatment period was separated by an interval of 5 days.

Part III evaluated the effects on nocturnal and meal stimulated acid secretions over a 22-hour interval with dosage regimens of famotidine 10 mg b.i.d., 20 mg b.i.d., 80 mg at 9:00 PM or placebo in an open-label design to 3 healthy volunteers. Each treatment period was separated by an interval of 5 days. Volunteers were acceptable for the study on the basis of a basal secretory rate greater than 5 mEq/h.

(4) Results: nocturnal acid output measured from 12 midnight to 7:00 AM after a dose of drug at 9:00 PM was inhibited by about 90% by both a 40 and 80 mg dose of famotidine.

(5) Conclusion: effective inhibition of nocturnal acid secretion can be achieved with a single oral dose of famotidine 40 mg h.s. The effect on food-stimulated secretion will be discussed under that heading.

c. Study No. 51

(1) Title: A double-blind, placebo-controlled, randomized 3-way cross-over study in ambulatory duodenal ulcer patients in remission to evaluate the effect of famotidine on 24 hour intragastric pH profile and concurrent gastrin values.

(2) Investigator: J. Lacey Smith, M.D., Baylor College of Medicine, Houston, TX.

(3) Design of Study: duodenal ulcer patients in remission with a basal acid secretion greater than 5 mEq/h were assigned randomly to receive either placebo at 9:00 AM and 9:00 PM, famotidine 20 mg at 9:00 AM and 9:00 PM or placebo at 9:00 AM and famotidine 40 mg at 9:00 PM. Study day 7 of each treatment period was designated as monitoring day during which the 24 hour intragastric profile was monitored continuously and blood samples collected for measurement of serum gastrin. On all monitoring days the patients were given a choice of foods from a menu providing for the same intake of xanthine-containing foods and beverages. Meal times were 8:30 AM, 12 M and 5:00 pm. Four subjects completed the study.

(4) Results

(a) Safety: no drug-related adverse events were reported.

(b) Nocturnal acidity (table 2): the median and ranges of pH measured from 1:00 AM to 9:00 AM were placebo 1.38 (1.20-2.38), famotidine 40 mg at 9:00 PM 5.88 (3.90-6.05) and famotidine 20 mg at 9:00 AM and 9:00 PM 5.53 (3.92-6.97).

TABLE 2

Effect of famotidine on nocturnal acidity
Famotidine or placebo given orally at 9:00 PM
Mean intragastric pH measurements, 1:00 AM - 9:00 AM

Patient	Famotidine 40 mg	Famotidine 20 bg	Placebo
1	6.05	6.97	1.38
2	3.90	4.94	1.20
3	5.80	3.92	2.38
5	5.95	6.11	1.38
Median	5.88	5.53	1.38
Range	3.90-6.05	3.92-6.97	1.20-2.38

(c) Food stimulated secretion is discussed below under IIC3a.

(5) Conclusion: in duodenal ulcer patients in remission, the pH of nocturnal gastric secretion was significantly higher in patients receiving famotidine than in those receiving placebo.

d. Summary of studies on nocturnal secretion: the proposed therapeutic doses of famotidine (40 h.s. for short-term treatment, 20 h.s. for prevention of recurrence) reduce nocturnal acid production by 85-95% and increase intragastric pH to as high as 4 to 7 compared to placebo levels up to 2.4.

3. Food-stimulated secretion

a. Study No. 7: this is the study described above (IIC2b) in which the effect on nocturnal secretion was reviewed.

(1) Results

(a) Safety: no serious adverse reactions attributable to famotidine were reported.

(b) Acidity: a significant increase in the pH following breakfast was observed as a carryover of the effect of the 20 mg b.i.d. and 40 mg h.s. doses compared to placebo (table 3). Neither the previous h.s. dose of 40 mg nor the dose of 20 mg at 9:00 AM had any effect on the pH following the evening meal.

TABLE 3

Effect of famotidine on acidity of food-stimulated gastric secretion

Patient	Mean intragastric pH 9:00 AM - 5:00 PM			5:00 PM - 1:00 AM		
	40 mg HS	20 mg BID	Placebo	40 mg HS	20 mg BID	Placebo
1	3.32	3.35	1.99	1.47	1.75	1.63
2	2.82	3.08	2.07	2.36	1.77	1.29
3	2.21	2.78	1.99	1.42	2.34	1.72
5	2.80	3.20	1.96	1.54	2.11	1.97
Median	2.81	3.14	1.99	1.51	1.94	1.68
Range	2.21-3.32	2.78-3.35	1.96-2.07	1.42-2.36	1.75-2.34	1.29-1.97

(c) Conclusion: a single h.s. dose of famotidine 20 or 40 mg has a moderate inhibitory effect on the gastric secretory response to breakfast on the following morning, but no effect on meals later in the day.

b. Study No. 51: the procedure and the effect on nocturnal secretion were reviewed above under IIC2c.

(1) Results

(a) Safety: the only clinical adverse experience occurred in a patient receiving placebo. The same subject also had an increase in band cells. One subject receiving famotidine 40 mg h.s. experienced transient pyuria, not considered drug-related.

(b) Effect on pH of digestive secretions: the mean pH measurements for each volunteer over the 9:00 AM to 5:00 PM interval were higher during administration of famotidine than during placebo, but the data were insufficient for statistical analysis.

c. Summary of studies on food stimulated secretion: insufficient data are available to permit conclusions regarding the effects of famotidine on food stimulated secretion in duodenal ulcer patients in remission. In healthy volunteers doses of 20 and 40 mg h.s. show a carry-over inhibitory effect on breakfast-stimulated acid output.

4. Gastric emptying and pancreatic secretion

a. Study No. 61

(1) Title of study: An open-label study to evaluate the effect of treatment with famotidine on gastric emptying and pancreatic exocrine secretion in healthy volunteers.

(2) Investigator: Richard Redinger, M.D., University of Louisville, Louisville, KY.

(3) Design of study: in 6 healthy male volunteers receiving famotidine 40 mg b.i.d for 7 days, labeled chicken pate in beef stew was used to measure the gastric emptying time of a solid meal, and pancreatic exocrine function was assessed by measuring volume, bicarbonate and amylase after intravenous secretin, before and after 7 days of treatment.

(4) Results

(a) Safety: No clinical adverse experiences or clinically important changes in laboratory parameters were observed.

(b) Gastric emptying: famotidine had no significant effect on gastric emptying.

(c) Pancreatic exocrine function: mean volume of secretion (figure 22) was not affected by famotidine; there was a trend towards a reduction in the output of bicarbonate (figure 23) and amylase (figure 24) but the differences were not significant.

Figure 22
Mean Cumulative Volume (ml) of Duodenal Juice

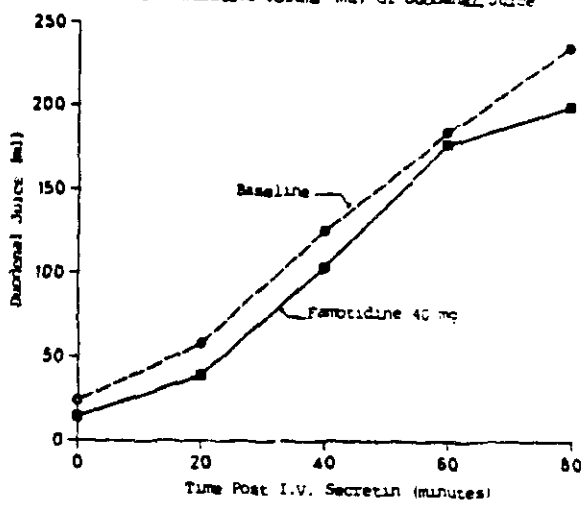


Figure 23
Bicarbonate, Mean Cumulative Total (mEq)

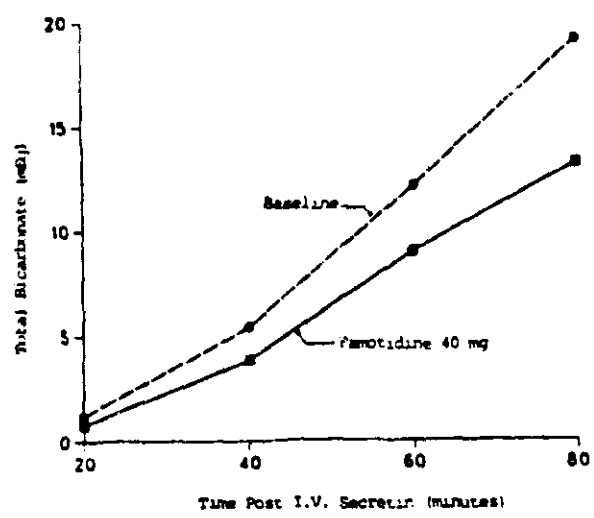
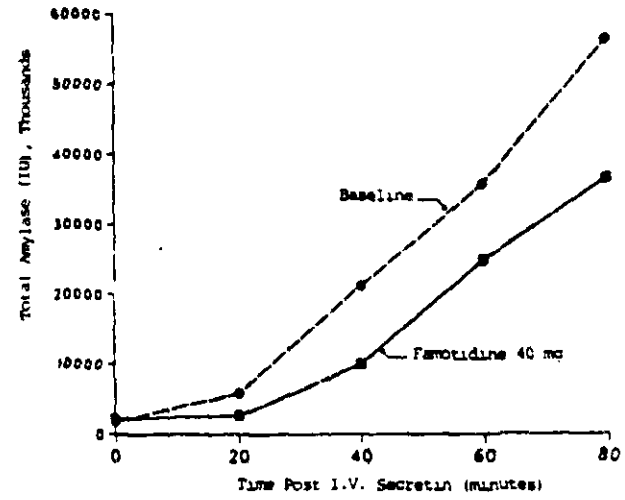


Figure 24
Amylase, Mean Cumulative Total (IU)



(d) Conclusion: on the basis of the limited amount of data available from this one study there appears to be no significant effect of famotidine on gastric emptying or pancreatic exocrine secretion.

(e) Comment: the trend toward reduction of volume and especially of bicarbonate output after administration of famotidine may indicate a real effect. The less acid reaching the upper intestine, the less release of secretin and the less stimulus to these functions of the pancreas. This possibility could be better evaluated by determining the effect of famotidine on the basal secretions of the pancreas.

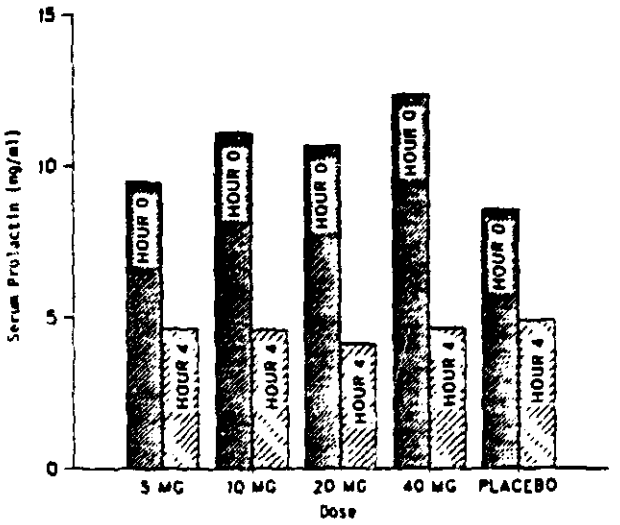
5. Summary of effects on gastric and pancreatic function: famotidine suppressed basal, food-stimulated nocturnal and pentagastrin stimulated volume and acidity of gastric secretion in a dose-related manner. The dose recommended for short-term treatment of peptic ulcer (40 mg h.s.) inhibited nocturnal secretion almost completely and had a significant carry-over effect on the acid response to a breakfast meal or an injection of pentagastrin secretion on the following morning. Pepsin concentration was not affected, but pepsin output was reduced in consequence of the reduction in volume of secretion. Famotidine had no effect on the rate of gastric emptying of a meal, nor, apparently, on secretin-stimulated pancreatic secretion.

D. Hormonal effects

1. Study No. 1: the protocol was described under "Human tolerance", (IIA2).

Effect on serum prolactin (figure 25): mean prolactin levels with all drug doses were higher at 0 hour than with placebo; these differences were thought to be attributable to the inherent variations of measurement. Four hours after dosing, significant mean decreases from 0 hour were observed for all treatments, probably reflecting diurnal variation.

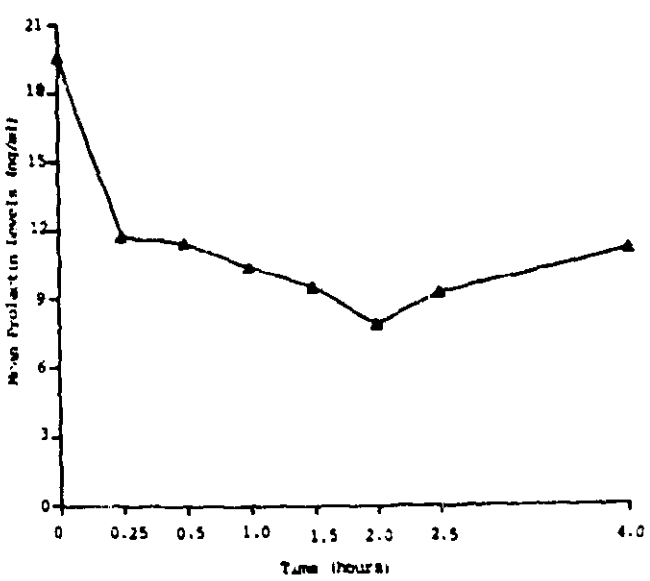
Figure25
Mean Serum Prolactin 0-4 Hours Post-Dose (N=15)



2. Study No. 42: the protocol was reviewed under "Human Tolerance" (IIA2).

Effect on secretion of prolactin (figure 26): prolactin levels assessed over a period of 4 hours following intravenous administration of famotidine 20 mg were significantly lower than the pre-drug levels. The sponsor speculates that this might be because the baseline blood samples were obtained immediately after the subjects had stopped being ambulatory, whereas the post-drug samples were obtained while the subjects had been recumbent for some time. Also, the known diurnal variation in serum prolactin levels may have been a factor. At any rate, famotidine 20 mg administered intravenously did not stimulate prolactin secretion.

Figure 26
Mean Prolactin Levels Following Intravenous Administration



3. Study No. 31

a. Title of study: A double-blind, dose-ranging study to evaluate the effects on healing of active duodenal ulcer, famotidine compared to placebo.

b. Investigator: Ram K. Shrivastava, M.D., New York, New York.

c. Design of study: an addendum was made to this study to include measurement of selected hormones. Blood samples were taken at baseline and at the end of the short-term treatment of duodenal ulcer for determination of prolactin, FSH and LH, gastrin, and, in males, testosterone.

d. Results: some or all of the parameters were tested in up to 10 patients. Minor changes, not clinically important, were recorded, suggesting that famotidine has no effect on the hormones measured.

e. Conclusion: in this limited number of subjects, there was no apparent drug-related effect on hormone levels.

4. Summary of hormonal affects: famotidine did not stimulate the release of prolactin, FSH, LH or testosterone. Since there were no comparative studies with other H_2-blockers, the significance of these findings is questionable. An inhibitory effect of famotidine on prolactin secretion is not ruled out by the data submitted.

E. Drug interactions

1. Study No. 48

a. Title of study: An open label, randomized, 2-way, cross-over study to assess the effect of famotidine and of cimetidine on the disposition of intravenous theophylline.

b. Investigator: Roger L. Williams, M.D., University of California, San Francisco, CA.

c. Design of study: an open, randomized, 2-way cross-over study in healthy volunteers to determine the effect of multiple oral doses of famotidine and cimetidine on the pharmacokinetics of intravenous theophylline as measured by plasma concentrations and urinary recovery.

The pharmacokinetics of famotidine after single and multiple doses were also examined. The study was carried out in 10 healthy volunteers, 5 of each sex, ages 21-32, mean 24.5 years. Each study period was of 9 days duration and divided into 3 parts. Part 1 was a baseline segment consisting of the initial 2 days in which aminophylline (85% theophylline) 5 mg/kg was administered IV and plasma and urine collected to establish

baseline concentrations of theophylline. Part 2 was a 1-day no-treatment washout segment. Part 3 was a drug treatment segment in which either famotidine 40 mg b.i.d. or cimetidine 300 mg q.i.d. was administered for 3 days and plasma and urine collected to establish single-dose and repeat-dose plasma concentrations of famotidine but not cimetidine. On the fourth day, aminophylline was given concomitantly with famotidine or cimetidine. Plasma and urine were collected for both drug groups for 48 hours and the findings compared with the baseline theophylline period. A minimum 7 day washout period separated the study periods. Adverse reactions were monitored throughout.

d. Results:

(1) Safety: no adverse clinical or laboratory events attributable to famotidine or cimetidine were reported.

(2) Disposition of theophylline: total body clearance of theophylline was unchanged by famotidine (58 vs 61 ml/min), but was significantly decreased by cimetidine (58 vs 40 ml/min), p 0.01. The half-life of theophylline remained constant during treatment with famotidine, but was significantly prolonged (9.3 to 12.2 h), p 0.05, with cimetidine. Plasma concentration (figure 27) and urinary excretion (figure 28) of theophylline remained unchanged during treatment with famotidine, but plasma concentration was increased and urinary recovery prolonged during treatment with cimetidine.

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Figure 27
Plasma concentration of Theophylline
After I.V. Administration of 5 mg/kg Theophylline

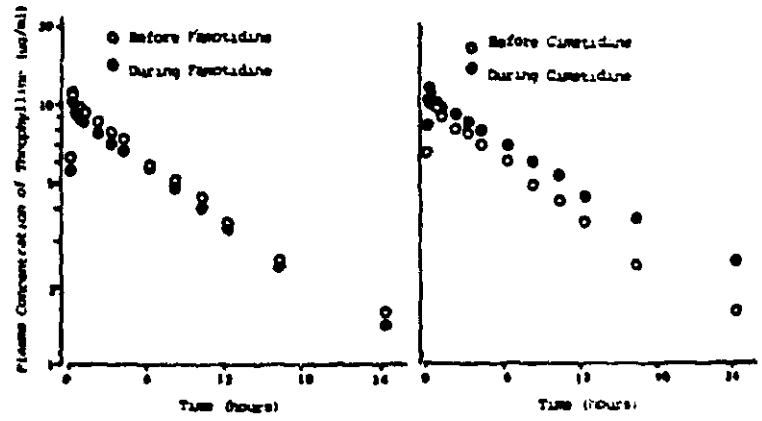
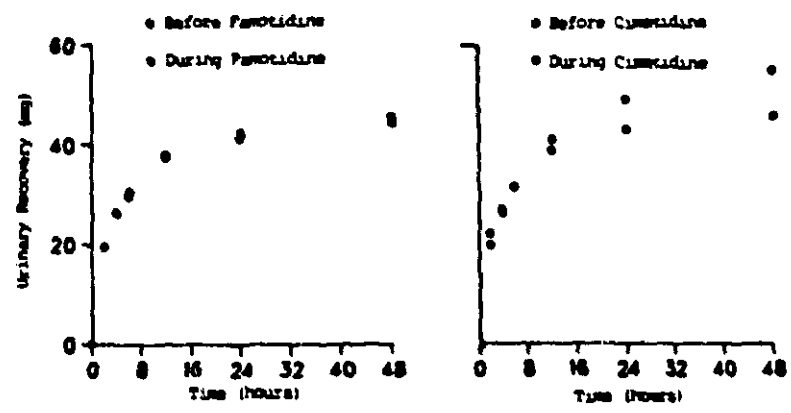


Figure 28
Cumulative Urinary Recovery of Theophylline After
I.V. Administration of 5 mg/kg Theophylline



e. Conclusion: cimetidine in therapeutic dosage, but not famotidine in higher than anticipated therapeutic dosage, decreased the metabolic elimination of theophylline.

2. Study No. 53

a. Title of study: Effect of famotidine on the anticoagulant action of sodium warfarin in healthy volunteers.

b. Investigator: Jerome R. Ryan, M.D., Clinical Research Center, New Orleans, LA.

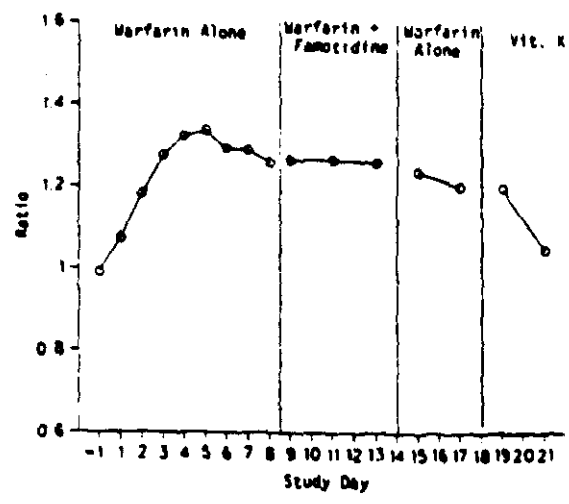
c. Design of study: 10 healthy male subjects participated. During Period I the subjects received a single-oral dose of sodium warfarin in the evening; prothrombin times (PTs) were determined in the morning. The dose of sodium warfarin was adjusted by the investigator so that the subjects were sub-therapeutically anti-coagulated, defined as a PT which was just a few seconds longer than the subject's baseline (a maximum of 2.5 x control). The subject was maintained on this dosage to insure that a steady state had been achieved, defined as PTs on 3 consecutive days within 15% of each other. During Period II the subjects received famotidine 40 mg orally morning and evening for 4.5 days, the last dose having been administered on the morning of the 5th day; the maintenance dose of sodium warfarin was continued once a day in the evening for 5 days. During Period III the subjects received their maintenance dose of sodium warfarin once a day in the evening for 5 days followed by a brief washout period during which no drug was administered. At the beginning of the washout period, subjects received a single 5 mg dose of vitamin K. The washout period lasted until the subject's PT value was within one second of the baseline. Throughout the investigation blood samples for determination for PTs were collected at intervals appropriate to the purpose of the investigation.

d. Results

(1) Safety: five subjects reported clinical adverse experiences; one (watery stool with gas) was considered possibly drug-related. The symptoms were in no instance severe and all resolved without residual effects. No subjects were discontinued because of adverse experiences. One subject had an elevation of SGPT to 71 units (ULN 45) at the end of the study; the subject was lost to follow-up.

(2) Effect on prothrombin time (figure 29): famotidine did not affect the prothrombin time in normal volunteers receiving warfarin (range 2-10 mg/day) plus famotidine 40 mg orally daily for 4.5 days.

Figure 29
Mean Prothrombine Time Ratios (N=10)



e. Conclusion: repeated administration of famotidine 40 mg b.i.d. for 4.5 days had no effect on the anticoagulant action of the sodium warfarin.

3. Study No. 55

a. Title of study: An open label, randomized, 2-way cross-over study to assess the effect of famotidine and of cimetidine on the disposition of oral phenytoin and on hepatic blood flow.

b. Investigator: Roger L. Williams, M.D., Drug Studies Unit, University of California, San Francisco, CA.

c. Design of Study: an open-label, randomized two-way cross-over study in 10 healthy volunteers, 8 men and 2 women ranging in ages from 20 to 47 years with a mean of 30.6 years, to examine the effects of repeated doses of cimetidine and of famotidine on the plasma kinetics of phenytoin given as a single oral dose and on the hepatic blood flow determined by the kinetics of indocyanine green (ICG) given intravenously. Part 1 of the study was a baseline segment consisting of 5 days in which oral phenytoin 100 mg and intravenous ICG 0.5 mg/kg were given on the morning of day 1 of the study. Blood and urine were collected for 96 hours to the morning of day 5. Part 2 was an 8-day drug-treatment period during which either famotidine 40 mg h.s. or cimetidine 300 mg q.i.d. were administered for 7 days from day 6 through day 12. Single doses of phenytoin 100 mg p.o. and ICG 0.5 mg/kg IV were given on the 3rd day of this period, i.e., day 9. Blood and urine samples were collected from the start of the phenytoin-ICG administration on study day 9 for 96 hours to the morning of study day 13. A minimum 14-day washout interval separated the 2 cross-over 13-day periods of the study. Phenytoin was given as Dilantin Capsules 100 mg p.o., ICG as a 10 second intravenous bolus.

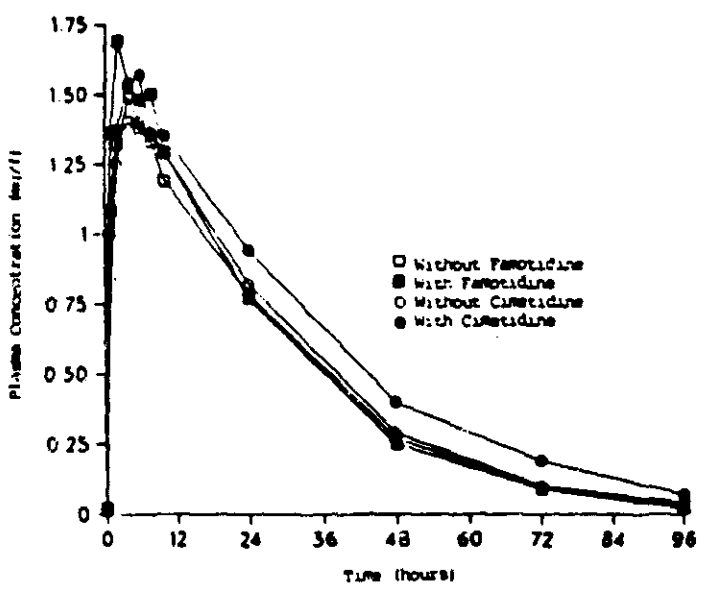
d. Results:

(1) Safety: no clinical or laboratory adverse events were reported.

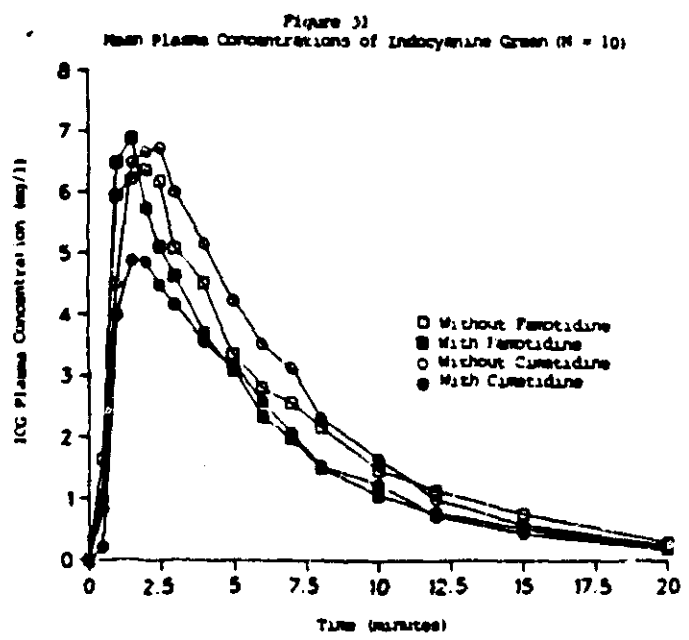
(2) Pharmacokinetic observations

(a) Disposition of phenytoin: plasma concentrations of phenytoin were increased by concurrent administration of cimetidine but not famotidine (figure 30).

Figure 30
Mean Plasma Concentrations of Phenytoin (N = 10)



(b) Hepatic blood flow: neither drug had a significant effect on hepatic blood flow as determined by clearance of ICG (figure 31).



e. Conclusion: in contrast to cimetidine, famotidine does not interfere with the biological disposition of phenytoin. Neither drug appears to affect hepatic blood flow.

4. Study No. 58

a. Title of study: An open label, randomized 3-way cross-over study to assess the effects of famotidine, cimetidine and no-drug treatment on the disposition of intravenous diazepam.

b. Investigators: Miguel A. Zinny, M.D., Medical and Technical Research Associates, Needham, MA, and David A. Greenblatt, M.D., Division of Clinical Pharmacology, Tufts-New England Medical Center, Boston, MA.

c. Design of study: open, randomized, 3-way cross-over study in 13 healthy male volunteers to determine the effect of famotidine and cimetidine on the pharmacokinetics of diazepam. Each of 3 study periods lasted for 8 days. On day 2 of each period, diazepam 10 mg was given as a single intravenous infusion over 15 to 30 seconds at approximately 8 am, following which blood samples were drawn at intervals up to 168 hours. The minimum washout interval between study periods was 3 weeks. Co-administration of the test drugs began on day 1 and consisted of either famotidine 40 mg b.i.d. or cimetidine 300 mg q.i.d. for 8 days. In the other segment, no drug treatment was given in connection with the injection of diazepam.

d. Results

(1) Safety: of the 13 volunteers enrolled, one was discontinued because of abnormal liver function findings pre-study; this volunteer was replaced by another who, however, was lost to follow-up after completing the first study period (cimetidine co-administration). The remaining 11 volunteers completed the 3 study periods. The safety data from this study are combined with safety data from a previous protocol designated Study No. 56, which was the same protocol but was not suitable for analysis of effectiveness because a period of no drug treatment had not been included. Three of the subjects participating in study no. 56 had mild elevations of SGPT during both the famotidine and cimetidine periods; 4 of the subjects in protocol 58 also had mild elevations of SGPT or SGOT during both drug periods and 2 of them also had elevated SGPTs during no drug treatment. Clinical adverse experiences occurred in 2 patients receiving cimetidine but were very unlikely to be drug-related. No other adverse events were reported.

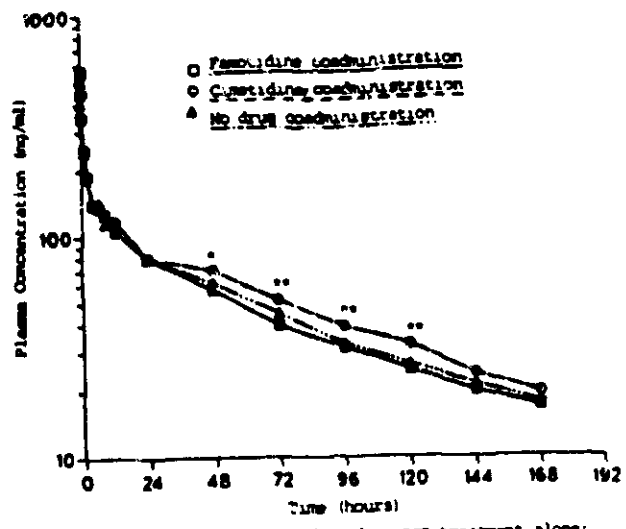
(2) Pharmacokinetics: co-administration of neither famotidine nor cimetidine influenced V_1 (apparent volume of distribution in the central compartment) or V_d (total apparent volume of distribution) of diazepam (table 4). However, cimetidine co-administration significantly prolonged the apparent diazepam elimination $t_{1/2}$ (half-life), increased AUC (total area under the plasma concentration time curve), reduced total clearance and increased the AUC of desmethyldiazepam. None of these effects were observed with co-administration of famotidine. Mean plasma concentrations of diazepam and desmethyldiazepam associated with co-administration of the respective treatments (figures 32 and 33) show that with cimetidine, but not with famotidine, there was a statistically significantly higher plasma concentration of diazepam from 24 through 120 hours and of its metabolite from 96 through 168 hours.

Table 4
Pharmacokinetic Parameters for Diazepam
and Desmethyldiazepam (mean ± SD)

		TREATMENT COADMINISTRATION					
PARAMETER	UNITS	FAMOTIDINE		CIMETIDINE		NO DRUG	
Diazepam							
V_1	liters/kg	0.21	(0.06)	0.2*	(0.05)	0.26	(0.14)
V_d	liters/kg	1.08	(0.36)	1.16	(0.3**)	1.17	(0.38)
$t_{1/2}$	hr	52.6	(25.5)	72.2 **	(31.8	54.7	(21.48)
Total AUC	mg/ml x hr	9.45	(3.96)	11.76 **	(3.08)	9.78	(4.11)
Clearance	ml/min/kg	0.277	(0.117)	0.201**	(0.054)	0.276	(0.128)
Desmethyldiazepam							
AUC Desmethyldiazepam	mg/ml hr	3.93	(0.78)	4.58*	(1.08)	3.84	(0.79)

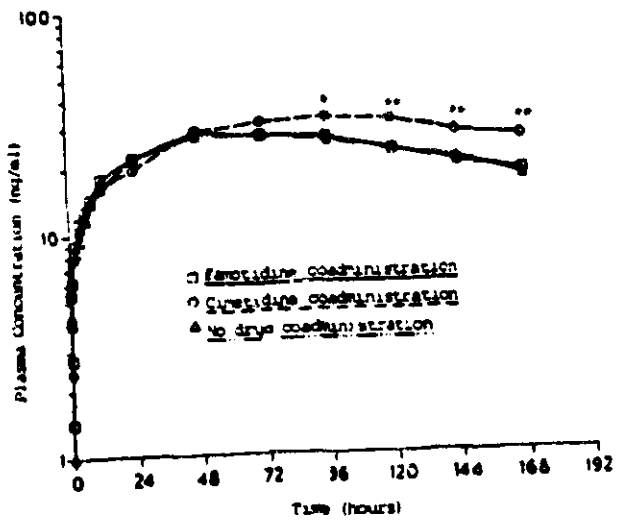
*,** Significantly different from diazepam treatment alone, $p < 0.05$, $p < 0.01$ respectively.
Note: No comparisons between MK-208 and cimetidine were performed.

Figure 32
Mean Plasma Concentrations of Diazepam (N=11)



Significantly different from diazepam treatment alone:
* $p<0.05$, ** $p<0.01$

Figure 33
Mean Plasma Concentrations of Desmethyldiazepam



Significantly different from diazepam treatment alone:
* $p<0.05$, ** $p<0.01$

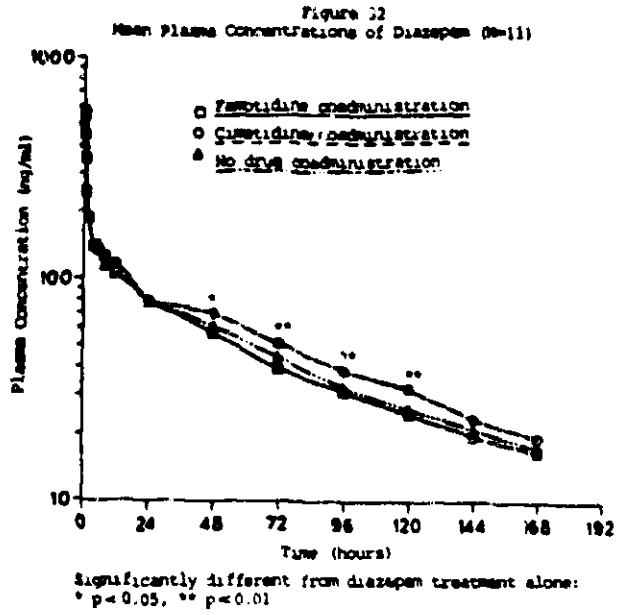
e. Conclusion: treatment with famotidine 40 mg b.i.d., a dose higher than the recommended therapeutic dose in the treatment of peptic ulcer disease, does not alter the biological disposition of diazepam or its active metabolite desmethyldiazepam while cimetidine, in conventional therapeutic dosage, does. Thus, in contrast with what is observed with cimetidine, no problem is expected in the concurrent administration of famotidine with diazepam.

5. Study No. 690

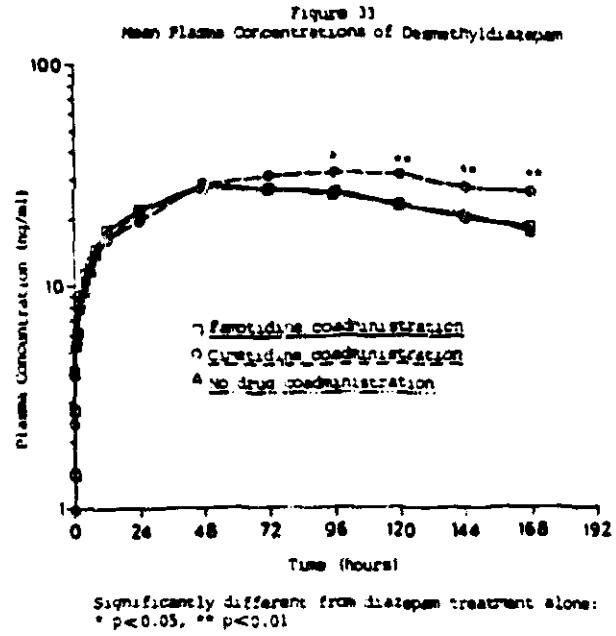
a. Title of study: Famotidine and hepatic drug metabolism.

b. Investigators: Professor M. J. S. Langman and Dr. K. W. Somerville, Department of Therapeutics, Nottingham Medical School, Nottingham, England.

c. Design of study: open label design evaluating the effect of multiple doses of famotidine on the hepatic metabolism of 8 healthy volunteer subjects. Once during the week prior to the start of famotidine treatment and on day 7 following the morning dose of famotidine each subject received antipyrine 1 g orally, immediately following which the subjects also received ^{14}C-aminopyrine 2 microcuries as an intravenous bolus. Saliva and breath samples were obtained from each subject at specified intervals during the pre-treatment baseline and on day 7. Famotidine 40 mg was administered before breakfast and before the evening meal. Samples of saliva were assayed for antipyrine concentration as an index of plasma antipyrine concentration. $^{14}CO_2$ dpm was measured by liquid scintillation counter to indicate the hepatic demethylation of aminopyrine.



Significantly different from diazepam treatment alone:
* $p < 0.05$, ** $p < 0.01$



Significantly different from diazepam treatment alone:
* $p < 0.05$, ** $p < 0.01$

e. Conclusion: treatment with famotidine 40 mg b.i.d., a dose higher than the recommended therapeutic dose in the treatment of peptic ulcer disease, does not alter the biological disposition of diazepam or its active metabolite desmethyldiazepam while cimetidine, in conventional therapeutic dosage, does. Thus, in contrast with what is observed with cimetidine, no problem is expected in the concurrent administration of famotidine with diazepam.

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d. Results

(1) Safety: one of the 8 subjects experienced mild diarrhea throughout the 7 days on famotidine; this subsided after the investigation was completed. Two of the subjects experienced mild fatigue th oughout the drug-taking phase of the investigation. One subject had a minor increase in SGPT at the end of treatment; the result of a repeat test 3 months later was normal.

(2) Hepatic drug metabolism: after 7 days of treatment with famotidine 40 mg b.i.d. the mean elimination half-life of antipyrine and aminopyrine decreased less than 10% from baseline.

e. Conclusions: the sponsor concludes, on the basis of a statistical analysis, that there is a 95% probability that the median increase from baseline levels in antipyrine half-life is less than 10% and an equal probability that the median increase in aminopyrine half-life is less than 25%.

f. Comment: in fact, one of the subjects showed an increase in the antipyrine half-life and 2 showed an increase in the aminopyrine half-life; consequently, it would appear valid to conclude that famotidine may, in some individuals, impair the oxidative metabolic functions of the liver.

6. Summary of results of studies on drug interactions: data submitted in this section are supported by a published paper (Staiger C et al, Arzneim Forsch 1984; 34:1041-1042) in concluding that famotidine does not affect oxidative metabolic functions of the liver. These observations are supported further in the results of studies showing absence of interaction of famotidine with diazepam, theophylline, phenytoin and warfarin. These data indicate that these drugs may be given without need for dosage adjustment in patients taking famotidine.

F. Ancillary studies

1. Study No. 12

a. A double-blind, dose-ranging study to evaluate the effects on healing of active duodenal ulcers with famotidine compared to placebo.

b. Investigator: Edward Cattau, Jr., M.D., National Naval Medical Center, Bethesda, MD.

c. Design of study: in the course of this clinical trial, samples of gastric secretions were obtained at the baseline endoscopy, at the end of the short-term study and at the end of 6 months (treatment was continued to evaluate prevention of recurrence). During endoscopy 5 ml of aspirate was collected in a sterile syringe for both qualitative and quantitative analysis of aerobic and anaerobic organisms.

d. Results: only 5 patients were evaluated, all during the short-term treatment period, and in only one patient was a change in gastric flora observed.

e. Conclusion: the data are insufficient to permit any conclusions regarding a possible famotidine-related effect on gastric flora.

III Clinical Trials

A. United States studies

1. Protocol No. 5006 (US multicenter trial)

a. Title of study: Famotidine in the short-term treatment of duodenal ulcer.

b. Design of the trial

(1) Admission criteria: patients with clinical symptoms of duodenal ulcer with an endoscopically demonstrated duodenal ulcer 0.5 to 2.5 cm in longest dimension.

(2) Exclusions

(a) Pyloric stenosis or peptic ulcer other than in the duodenal bulb
(b) Zollinger-Ellison syndrome
(c) Complications such as perforation or gross hemorrhage within 7 days
(d) Treatment with anticholinergics or H_2-blockers within the previous week
(e) Concomitant significant disease
(f) Lactation or child-bearing potential.

(3) Clinical observations: history of previous peptic ulcer disease, alcohol and smoking habits, physical examination, ECG, conventional clinical laboratory tests and upper endoscopy to confirm the presence of duodenal ulcer(s). Follow-up assessments of clinical symptoms were made and endoscopies performed at weeks 2, 4 and 8. Once ulcer healing was demonstrated at any of these intervals, the patients were eligible to be re-randomized into a 1 year maintenance study. Those whose ulcers had not healed at the end of 8 weeks were considered to have completed the study as a treatment failure. At each treatment visit the patients were given diary cards for daily recording of day and night pain, gastrointestinal symptoms, number of antacid tablets taken and any adverse experiences. The data from these diaries were reviewed at each visit. At the completion of the study the physical and laboratory examinations were repeated.

(4) Treatment schedules: patients were randomized to one of the following 4 dosage regimens.

(a) Famotidine 40 mg, h.s. (placebo at 8:00 am, famotidine at 10:00 pm)

(b) Famotidine 20 mg b.i.d., 8:00 AM and 10:00 PM

(c) Famotidine 40 mg b.i.d., 8:00 AM and 10:00 PM

(d) Placebo at 8:00 AM and 10:00 PM

(5) Antacids: each patient received a bottle of antacid tablets to be taken only if additional symptomatic relief was required.

c. Evaluation criteria

(1) Endoscopy

(a) Normal: no ulcer present, complete epithelization of the ulcer crater, regardless of the persistence or emergence of duodenitis and/or erosions.
(b) Ulcer: incomplete epithelization of the ulcer.

(2) Pain. severity of day and night pain was recorded by the patient on a scale of 0 = none, 1 = mild, 2 = moderate and 3 = severe. The terms were not defined.

(3) Patients' assessments of global response to therapy were graded 0 = none, 1 = poor, 2 = fair and 3 = good and 4 = excellent, again without definition of the terms.

(4) Safety: adverse clinical and laboratory events were recorded and evaluated by the investigator as to severity, seriousness, relationship to study drug and outcome.

d. Statistical treatment: the analysis of effectiveness at each time point was done as an "end point" analysis, i.e., patients whose ulcers healed at weeks 2 or 4 actually completed the study per protocol and subsequently did not have data. The specific methods of analysis of the data are indicated in the tabulations of the results. Validity of the statistical methods applied by the sponsor in this and subsequent trials is the subject of a separate review of this NDA by FDA biometricians.

e. Investigators (table 5): all of the physicians participating in this clinical trial are well-qualified by training and experience to undertake studies of this type.

Table 5

Name/Study No.	Affiliation	Location
Elliot Alpert, M.D./43	Methodist Hospital	Houston, Texas 77030
Robert H. Bishop, Jr.,M.D./10	3266 N. Meridian Street	Indianapolis, IN 46208
James H. Butt III,M.D./11	Veterans Administration Hospital	Columbia, MO 65212
James Campbell, M.D./22	University of Nebraska Med.Ctr.	Omaha, Nebraska 68105
Edward L. Cattau, Jr., M.D./12	National Naval Medical Center	Bethesda, Maryland 20014
William Engel, M.D./16	St. Vincent's Hospital	Indianapolis, IN 46260
Norman Gitlin, M.D./13	Veterans Admin. Hospital	Fresno, CA 93703
Daniel Pelot, M.D./14	University of California	Irvine, CA 92717
Shahenawaz Jaffer, M.D./19	Magan Medical Clinical Inc.	Covina, CA 91723
James H. Johnson, M.D./17	Watson Clinic	Lakeland, FLA 33801
R. Bruce Johnson, M.D./15	Rees-Steely Medical Group	San Diego, CA 92101
James F. King, M.D./18	Gastroenterology Associates	Canton, Ohio 44708
Stephen M. Levine, M.D./35	1210 Brace Road	Cherry Hill, NJ 08034
Ross Madden, M.D./49	Medical Associates Clinic, P.C.	Dubuque, Iowa 52001
Arthur J. McCullough, Jr., M.D./44	Metropolitan General Hospital	Cleveland, Ohio 44109
Frank Mico, M.D./24	Fullerton Internal Medicine Clinic	Fullerton, CA 92635
William A. Milhon, M.D./23	3730 Olentangy River Road	Columbus, OH 43214
Richard Redinger, M.D./25	University of Louisville	Louisville, KY 40202
Allen Rubin, M.D./21	5959 Harry Hines Blvd.	Dallas, TX 75235
Ivan Rudolph, M.D./26	Brachfeld Medical Associates	Willingboro, NJ 08046
Cesar Ruzzit, M.D./46	Washington Center for Clinical Studies	Washington, DC
Ram Shrivastava, M.D./31	Eastside Comprehensive Medical Services	New York, NY 10021
J. Lacey Smith, M.D./28	Veterans Admin. Medical Center	Houston, TX 77211
Joseph Speer, M.D./37	6004 Ventnor Ave.	Ventnor City, NJ 08406
E.Clinton Texter,M.D./29	Univ. of Arkansas for Medical Sciences	Little Rock, AR 72205
Joycelyn Theard, M.D./45	San Antonio Center for Clinical Studies	San Antonio, TX 78217
Fred B. Thomas, M.D./09	Ohio State University	Columbus, OH 43210
Ronald Thune, M.D./50	West Side Clinic, S.C.	Green Bay, WI 54303
Jorge Valenzuela, M.D./38	U.S.C. Medical Center	Los Angeles, CA 90033
Stephen D. Ward, M.D./34	1245 Highland Ave.	Abington, PA 19001
Robert W. Lufkin, M.D./30	Florida Center for Clinical Studies	St.Petersburg, FL 33701
Dominic Wong, M.D./27	Henry Ford Hospital	Detroit, MI 48202
Herbert A. Yantes, M.D./57	Phila. Center for Clinical Studies	Philadelphia, PA 19152
Alvin M. Zfass, M.D./32	Medical College of Virginia	Richmond, VA 23298

f. Results

(1) Comparability of treatment groups (table 6): the 4 treatment groups were comparable in all essential characteristics.

TABLE 6

Comparability of Treatment Groups, number 8

	FAMOTIDINE 40 HS (n=96)	FAMOTIDINE 20 BID (n=89)	FAMOTIDINE 40 BID (n=99)	Placebo (n=100)
Age Mean	45.6	47.3	43.6	46.4
Sex Males Females	75 (78) 21 (22)	69 (78) 20 (22)	81 (82) 18 (18)	76 (76) 24 (24)
Weight (lb.)	167.9	171.9	170.1	166.5
Smoking	58 (60)	52 (58)	59 (60)	61 (61)
Alcohol	18 (19)	12 (13)	14 (14)	13 (13)
Caffeine	56 (58)	59 (66)	62 (63)	59 (59)
Initial Ulcer Size (cm)[a] Mean	0.86	0.93	0.88	0.86
Number of Ulcers One Two or more	79 (82) 17 (18)	73 (82) 16 (18)	88 (89) 11 (11)	82 (87) 13 (13)
Age at First Ulcer Mean	37.9	40.6	35.8	39.7
Duration of Ulcer H_x (yrs) Mean	7.7	6.7	7.8	6.7
Ulcer History None Single Multiple	30 (31) 22 (23) 44 (46)	42 (47) 19 (21) 28 (31)	34 (34) 24 (24) 41 (42)	26 (26) 30 (30) 44 (44)
Other pathology in esophagus	24 (25)	27 (30)	20 (20)	33 (33)
Other pathology in stomach	32 (33)	25 (28)	32 (32)	31 (31)
Other pathology in duodenum	63 (66)	50 (56)	61 (62)	63 (63)
Concomitant diseases Cardiovascular Respiratory Gastrointestinal Musculoskeletal Endocrine Other	7 (7) 4 (4) 9 (9) 5 (6) 5 (5) 4 (4)	9 (10) 4 (4) 10 (11) 10 (11) 2 (2) 7 (8)	11 (11) 6 (6) 9 (9) 6 (6) 5 (5) 7 (7)	7 (7) 3 (3) 13 (13) 2 (2) 8 (8) 7 (7)

[a]For patients with more than one ulcer, this was the size of the largest ulcer. No significant differences were observed.

(2) Safety

(a) Vital signs (table 7): there was a statistically significant decrease in the mean pulse rate in patients receiving 40 mg b.i.d. and in the mean systolic blood pressure in patients receiving 40 mg h.s; these changes are not, however, of any clinical significance.

TABLE 7

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE FROM BASELINE
Pulse rate (beats/min.)	40 HS	94	75.9	74.5	-1.3
	20 BID	86	76.7	75.4	-1.3
	40 BID	95	76.8	73.0	-3.8+,**
	Placebo	97	76.1	76.7	0.6
Systolic BP (mmHg)	40 HS	96	122.4	119.5	-2.9*
	20 BID	87	123.5	124.8	1.3
	40 BID	95	123.1	123.5	0.4
	Placebo	97	125.0	123.3	-1.7
Diastolic BP (mmHg)	40 HS	96	77.3	76.9	-0.4
	20 BID	87	77.4	78.2	0.8
	40 BID	95	78.7	78.4	-0.3
	Placebo	97	77.6	78.0	0.4
Weight (lbs.)	40 HS	91	167.9	168.5	0.6
	20 BID	83	171.9	172.1	0.2
	40 BID	91	170.1	170.1	-0.1
	Placebo	89	166.5	167.0	0.5

*,**Significant change from baseline, $p \ll .05$, $p \ll .01$, respectively.
+Significantly different from placebo, $p \ll .01$.

(b) Laboratory adverse events: in patients on famotidine there were no serious abnormal laboratory values; no patient receiving famotidine was withdrawn because of an adverse laboratory event. The one patient with a laboratory finding considered serious was on placebo.

(c) Clinical adverse experiences: the percentage of patients with adverse signs/symptoms (table 8) regardless of drug-relationship was no greater with famotidine treatment (27%) than with placebo (39%). The incidence of adverse experiences in patients 60 years or older was not different from that in the general population.

TABLE 8

Number Of Patients With Clinical Adverse Events (%)*

BODY SYSTEM	Famotidine 40 HS N = 96	Famotidine 20 BID N = 89	Famotidine 40 BID N = 99	PLACEBO N = 100
Central Nervous System				
Dizziness	0	3 (3)	1 (1)	4 (4)
Fatigue	1 (1)	2 (2)	1 (1)	1 (1)
Headache	5 (5)	8 (9)	9 (9)	11 (11)
Insomnia	0	2 (2)	0	2 (2)
Nervousness	0	1 (1)	2 (2)	2 (2)
TOTAL	6 (6)	16 (18)	13 (13)	20 (20)
Cardiovascular				
Thrombo- or phlebitis	0	0	2 (2)	4 (4)
Digestive				
Abdominal Pain	0	1 (1)	0	2 (2)
Anorexia	2 (2)	1 (1)	2 (2)	0
Constipation	3 (3)	1 (1)	2 (2)	1 (1)
Diarrhea	2 (2)	3 (3)	1 (1)	5 (5)
Dyspepsia	2 (2)	0	1 (1)	0
Flatulence	2 (2)	0	0	2 (2)
G.I. Hemorrhage	4 (4)	0	0	1 (1)
Nausea	2 (2)	1 (1)	0	3 (3)
TOTAL	17 (18)	7 (8)	6 (6)	14 (14)
Respiratory System				
Common Cold	0	3 (3)	0	0
Cough	0	2 (2)	0	0
Pharyngeal Pain	0	2 (2)	0	1 (1)
TOTAL	0	7 (8)	0	1 (1)
Tegumentary				
Hyperhydrosis	0	0	2 (2)	0
TOTAL	23 (24)	30 (34)	23 (23)	39 (39)

*Adverse experiences with an incidence of at least 2% in at least one of the treatment groups are displayed in this table

A more meaningful analysis lists the patients withdrawn from treatment because of adverse signs/symptoms (table 9); here the incidence seems appreciable (2-3% on drug, 5% on placebo) but many of these adverse occurrences represent complications of the underlying peptic ulcer disease. In evaluating the possible drug-relationship of these occurrences I have chosen to classify the sponsor's "probably not" as "possibly yes". Even with this "strict construction" it is clear that in this clinical trial famotidine appears to be a relatively safe drug.

TABLE 9

Patients Withdrawn because of Adverse Signs/Symptoms

TREATMENT	ALLOC	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	TOTAL POSSIBLY/PROB DRUG-RELATED
Famotidine 40 HS	1218	Gastric Ulcer	Severe	Probably not[a]	
		Hematemesis	Severe	Probably not	
	1216	Herpes Zoster	Severe	Probably not	
	1635	G.I. Hemorrhage	Severe	Def. not	
		Hematemesis	Severe	Def. not	
		Syncope	Severe	Def. not	
	1604	G.I. Hemorrhage	Moderate	Possibly	3/96 (3%)
Famotidine 20 BID	1257	Gastric Ulcer	Mild	Possibly	
	1539	Asthma	Severe	Probably not	
	1576	G.I. Pain	Moderate	Probably not	
		Nausea	Moderate	Probably not	
		Vomiting	Moderate	Probably not	3/89 (3%)
Famotidine 40 BID	1698	Grand mal Seizures	Severe	Possibly	
	1090	Conjunctival Inj.	Mild	Probably	
		Orbital Edema	Mild	Probably	2/99 (2%)
PLACEBO	1521	Vomiting	Severe	Def. not	
	1123	Chest Pain	Moderate	Probably not	
	1432	Gastric Ulcer	Mild	Possibly	
	1126	Headache	Mild	Possibly	
		Nausea	Mild	Possibly	
		Vomiting	Mild	Possibly	
	1215	Asthenia	Moderate	Possibly	
		Headache	Mild	Possibly	
		Abdominal Swelling	Moderate	Possibly	
		Constipation	Moderate	Possibly	
	1875	Gastric Ulcer	Mild	Possibly	5/100 (5%)

[a] "Probably not" = "Possibly yes"

(3) Effectiveness

(a) Number of patients evaluable: patients omitted from analysis of effectiveness (table 10) were remarkably few (22/384, 6%) considering the large number of patients entered in each treatment group. These non-cooperative patients or investigators (protocol violations, off drug) were identified early in the trial so that very few were lost after week 2. As might be expected, discontinuation because of ineffective therapy was highest in the placebo group (13%), but less expected was the high incidence (8%) of discontinuation because of adverse experiences.

Table 10
Number of Patients in Analysis of Results

	WEEK 2				WEEK 4				WEEK 8			
	Famotidine				Famotidine				Famotidine			
	40 HS	20 BID	40 BID	PBO	40 HS	20 BID	40 BID	PBO	40 HS	20 BID	40 BID	PBO
Total Entered	96	89	99	100	96	89	99	100	96	89	99	100
Patients with Incomplete Data												
Discontinued Adverse Experience	3	2	1	2	3	2	2	7	4	3	2	8
Discontinued Ineffective Therapy	0	1	1	6	1	1	1	10	1	1	1	13
Discontinued Other	3	3	3	4	5	4	8	10	5	4	8	10
Protocol Violations[b]	4	4	6	3	4	4	6	3	4	4	6	3
Off Drug[b]	2	0	0	0	3	1	0	0	3	1	0	0
No Treatment Data[c]	4	3	5	0	3	2	5	0	3	2	5	0
Total Included[a]												
Ulcer Healing	90	85	93	97	89	84	93	97	89	84	93	97
Day/Night Pain	86	82	88	97	86	82	88	97	86	82	87	86

[a] Patients who dropped out, were out of range, etc. had their last valid values carried forward to subsequent timepoints.
[b] Not included in per protocol ulcer healing and day/night pain analysis.
[c] Not included in per protocol day/night pain analysis.

(b) Incidence of healing: the sponsor tabulates the incidence of healing at weeks 2, 4 and 8; week 2 included endoscopies performed up to 18 days on treatment, week 4 up to 34 days and week 8 up to 65 days. The results (table 11) leave no doubt that all three doses of famotidine yield a similar incidence of healing and all are significantly more effective than placebo.

Table 11
Cumulative Number Healed/Number in Treatment Group (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=89	Famotidine 20 BID N=84	Famotidine 40 BID N=93	Placebo N=97
2 (Days 1-28)	28 (32)	32 (38)	31 (33)	16 (17)
4 (Days 19-34)	62 (70)	56 (67)	69 (74)	30 (31)
8 (Days 35-64)	74 (83)	69 (82)	75 (81)	44 (45)
Beyond Week 8 (Days 65-85)	75 (84)	69 (82)	76 (82)	44 (45)

At each time point, each of the famotidine treatment groups had a significantly higher healing rate than placebo, p<.001.

Since, however, demonstration of healing after 34 days of treatment is manifestly not proof of healing within 4 weeks, I requested the sponsor to tabulate the incidence of healing by actual weeks. This tabulation (table 12) shows that if the first follow-up endoscopy is performed at 5 weeks, a significantly smaller percentage of patents will require further treatment and an additional endoscopy. With the recommended dose (40 mg h.s.) the incidence of healing at 5 weeks was 70% compared to 53% at 4 weeks; with 40 mg b.i.d., the incidence of healing at 5 weeks was 75% compared to 54% at 4 weeks.

TABLE 12

Cumulative Number Healed (%)

Weeks (Day Range) on Treatment	Famotidine 40 HS N=89	Famotidine 20 BID N=84	Famotidine 40 BID N=93	Placebo N=97
Week 1 (Days 2-8)*	0 (0)	0 (0)	0 (0)	1 (0)
Week 2 (Days 9-15)	21 (24)	26 (30)	20 (22)	8 (8)
Week 3 (Days 16-22)	31 (35)	35 (42)	32 (34)	16 (16)
Week 4 (Days 23-29)	47 (53)	49 (58)	50 (54)	24 (25)
Week 5 (Days 30-36)	62 (70)	57 (68)	70 (75)	30 (31)
Week 6 (Days 37-43)	62 (70)	59 (70)	70 (75)	30 (31)
Week 7 (Days 44-50)	63 (71)	59 (70)	70 (75)	30 (31)
Week 8 (Days 51-57)	70 (79)	62 (74)	72 (77)	39 (40)

* Day 1 was the day of the baseline evaluation. Patients started taking drug at bedtime on day 1. All weekly day ranges start with day 2.

Among the 5 investigators who contributed at least 20 patients there was generally not much treatment-by-investigator interaction (table 13) except as regards placebo incidence of healing which varied from 10 to 60% at 4 weeks, 33-80% at 8 weeks. This is not a novel observation.

TABLE 13

Number (%) Healing Reported by Investigators with at Least 20 Patients --Number (%) Healed

Inv.	Famotidine 40 HS N	Wk 2	Wk 4	Wk 8	Famotidine 20 BID N	Wk 2	Wk 4	Wk 8	Famotidine 40 BID N	Wk 2	Wk 4	Wk 8	Placebo N	Wk 2	Wk 4	Wk 8
1	6	0 (0)	1 (17)	6(100)	4	2 (50)	3 (75)	3 (75)	5	2 (40)	4 (80)	5(100)	5	1 (20)	3 (60)	4 (80)
2	7	2 (29)	5 (71)	5 (71)	7	2 (29)	3 (43)	5 (71)	6	3 (50)	5 (83)	5 (83)	7	2 (29)	3 (43)	3 (43)
3	10	3 (30)	5 (50)	5 (50)	8	4 (50)	5 (63)	6 (75)	9	0 (0)	8 (89)	9(100)	10	1 (10)	1 (10)	4 (40)
4	8	4 (50)	8 (100)	8(100)	9	3 (33)	5 (56)	5 (56)	6	1 (17)	3 (50)	3 (50)	9	1 (11)	2 (22)	4 (44)
5	7	4 (57)	6 (86)	7(100)	8	3 (38)	7 (88)	8(100)	7	5 (71)	7(100)	7(100)	9	3 (33)	3 (33)	3 (33)
SUBTOTAL	38	13 (34)	25 (66)	31 (82)	36	14 (39)	23 (64)	27 (75)	33	11 (33)	27 (82)	29 (88)	40	8 (20)	12 (30)	18 (45)
*Pool	51	15 (29)	37 (73)	43 (84)	48	18 (38)	33 (69)	42 (88)	60	20 (33)	42 (70)	46 (77)	57	8 (14)	18 (32)	26 (46)
TOTAL	89	28 (32)	62 (70)	74 (83)	84	32 (38)	56 (67)	69 (82)	93	31 (33)	69 (74)	75 (81)	97	16 (16)	30 (31)	44 (45)

*All Other Investigators Combined.

(c) Effect of treatment on duodenitis/erosions: duodenitis and/or erosions co-existed with the duodenal ulcers in 201/363 (55%) of patients in whom such information was available at the pre-treatment endoscopy. Some observers consider the presence of duodenitis and/or erosions part of the spectrum of peptic ulcer disease. It is therefore of interest to evaluate the effect of treatment on these lesions and any effect their presence may have on ulcer healing (table 14). Among patients in whom the endoscopic records included reports of the presence or absence of duodenitis and/or erosions both before and after treatment in the same patients, the post-treatment incidence of duodenitis and/or erosions in patients in whom these lesions were not present pre-treatment was 24/78 (31%) on famotidine, 11/32 (34%) on placebo; the emergence of these lesions during treatment had no effect on healing of the ulcers. In patients in whom duodenitis and/or erosions were present pre-treatment, such lesions persisted in 84/146 (58%) on drug, 38/54 (72%) on placebo; the persistence of these lesions had no effect on the healing of the ulcers.

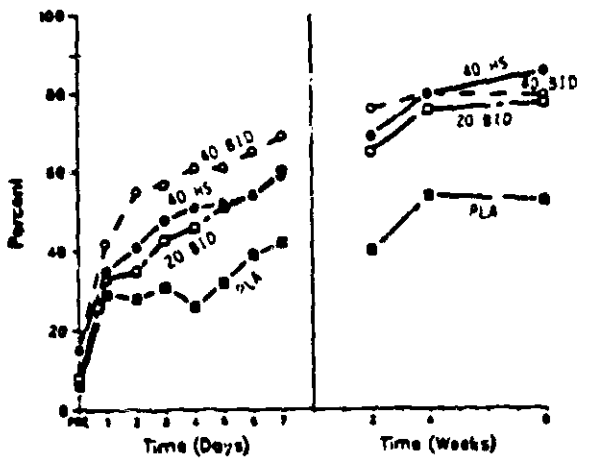
TABLE 14

Effect of Treatment on incidence of duodenitis/erosions and relation to healing of ulcer

	Duodenitis and/or erosions post-treatment and percent ulcers healed																			
	FAMOTIDINE										TOTAL				PLACEBO			
Duodenitis/ erosions pre-treatment	n	%	Ulcer Healed	%	n	%	Ulcer Healed	%	n	%	Ulcer Healed	%	n	%	Ulcer Healed	%	n	%	Ulcer Healed	%
None	11/24	46	11/11	100	6/28	21	5/6	83	7/26	27	7/7	100	24/78	31	23/24	96	11/32	34	4/11	36
Duodenitis/ erosions	32/63	51	26/32	81	26/43	60	21/26	81	26/51	51	23/26	88	84/147	58	70/84	83	39/54	72	19/39	49
TOTAL	43/87	49	37/43	86	32/71	45	26/32	81	33/77	43	30/33	91	108/225	48	93/108	86	50/86	58	23/50	46

(d) Relief of pain: the proportion of patients relieved of day pain was higher at all time points from the 3rd day onward through 8 weeks with all doses of famotidine than with placebo (figure 34). The proportion of patients relieved of night pain at the end of the first week was higher with the 40 mg h.s. and 40 mg b.i.d. doses than with 20 mg b.i.d. or placebo; from the second week onward, proportionately more patients receiving any dose of famotidine were relieved of night pain than were those receiving placebo (figure 35). The median number of days to relief of pain was significantly fewer with all doses of famotidine than with placebo (table 15).

Figure 34
Percentage of Patients With No Day Pain



Percentage of Patients With No Night Pain
Fig. 8.5
Percentage of Patients with No Night Pain

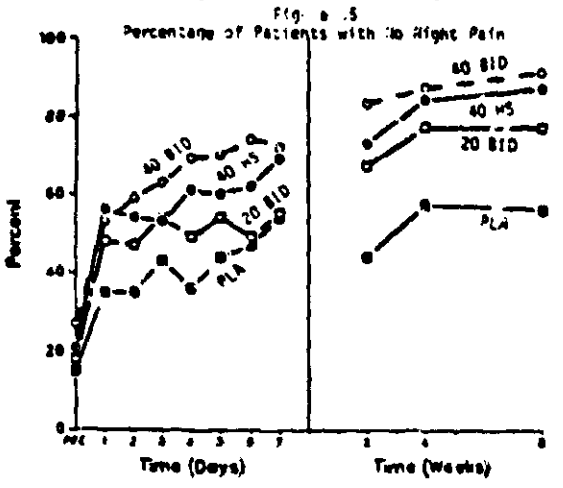


Table 15
Incidence, and Median Time to, Relief of Pain (Days)

		FAMOTIDINE 40 HS (n = 89)	FAMOTIDINE 20 BID (n = 84)	FAMOTIDINE 40 BID (n = 93)	PLACEBO (n = 97)
	Day Pain				
Incidence (%)		76 (85)	77 (92)	78 (84)	91 (94)
Baseline =	None[a]	10 (n = 13)	[illegible] (n = 7)	13 (n = 15)	22 (n = 6)
	Mild	6 (n = 23)	13 (n = 18)	4 (n = 25)	64 (n = 29)
	Moderate	14 (n = 35)	14 (n = 36)	10 (n = 39)	55 (n = 37)
	[illegible]	12 (n = 18)	20 (n = 23)	10.5 (n = 14)	27 (n = 25)
	[illegible]	11 (n = 89)	14.5 (n = 84)	9 (n = 93)	54 (n = 97)
	Night Pain				
Incidence (%)		76 (85)	68 (81)	65 (70)	82 (85)
Baseline =	None[a]	6.5 (n = 13)	6.5 (n = 16)	2 (n = 27)	11 (n = 15)
	Mild	10 (n = 21)	16 (n = 16)	2 (n = 17)	34.5 (n = 20)
	Moderate	9 (n = 33)	21 (n = 29)	9.5 (n = 28)	64 (n = 33)
	Severe	19 (n = 15)	11 (n = 23)	22 (n = 20)	54 (n = 29)
	Total	10 (n = 89)	14.5 (n = 84)	5.5 (n = 92)	52 (n = 97)

[a] Some patients had no pain at baseline but had pain at one or more subsequent timepoints. A significant within-group change from baseline was observed for each treatment group, $p<.01$. For both relief of Day Pain and relief of Night Pain, each of the famotidine groups were significantly better than placebo, $p < .001$.

(e) Antacid consumption: throughout most of the 8 weeks of the trial, the percentage of patients taking antacids was higher in the placebo-treated than in the famotidine-treated patients (figure 36). The mean number of days of antacid therapy (table 16) and the mean number of antacid tablets taken daily (table 17) were statistically significantly fewer at most intervals with famotidine than with placebo, but the differences were not clinically significant. For example, patients on placebo took less than one antacid tablet per day fewer throughout the 8 weeks of treatment than did the patients receiving famotidine 40 mg h.s., the dose recommended for the short-term treatment of duodenal ulcer. The mean number of days in which patients took antacids was less than one day more over an 8 week period with placebo than with the 40 mg h.s. dose.

Figure 36
Percentage of Patients Receiving Antacid Therapy

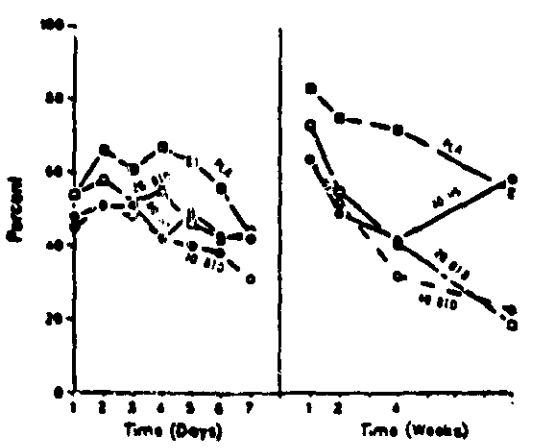


TABLE 16

Mean Days of Antacid Therapy, Mean ± Standard Deviation

	FAMOTIDINE 40 HS		FAMOTIDINE 20 BID		FAMOTIDINE 40 BID		PLACEBO		NUMBER OF DAYS DIFFERENCE BETWEEN 40 HS & PLACEBO
WEEK	N	MEAN	N	MEAN	N	MEAN	N	MEAN	
1	99	3.3 ± 3.06	84	3.5 ± 2.80	93	2.9 ± 2.86**	98	4.1 ± 2.64	-0.8
2	87	2.7 ± 3.05**	80	2.5 ± 2.81**	84	2.0 ± 2.53**	95	3.6 ± 2.79	-0.9
4	56	2.2 ± 2.87**	45	1.9 ± 2.69**	51	1.3 ± 2.28**	70	3.3 ± 2.67	-1.1
8	21	2.9 ± 2.98	18	1.0 ± 2.22**	12	0.8 ± 1.42**	37	2.8 ± 2.89	+0.1

** Significantly different from placebo, p<.01.
* Significantly different from 20 BID, p<.05 and significantly different from 40 BID, p .05.

TABLE 17

Number of Antacid Tablets Taken Daily, Mean ± Standard Deviation

	Famotidine 40 HS		Famotidine 20 BID		Famotidine 40 BID		Placebo		Difference Between 40 HS & Placebo
Week	N	Mean	N	Mean	N	Mean	N	Mean	
1	92	1.7±2.15**	84	1.9±2.35	93	1.5±2.15**	98	2.2±2.06	-0.5
2	87	1.4±1.99**	80	1.2±1.90**	84	0.9±1.61**	95	2.1±2.34	-0.9
4	56	1.0±1.71**	45	1.0±1.87**	51	0.6±1.23**	70	1.7±1.94	-0.7
8	21	1.2±1.41	18	0.7±2.13**	12	0.3±0.71*	37	1.6±1.79	-0.2

*,** Significantly different from placebo, p<.05, p<.01, respectively.

(g) Summary: this trial of the short-term (up to 8 weeks) healing of duodenal ulcer compared famotidine in doses of 40 mg h.s., 20 mg b.i.d. and 40 mg b.i.d. with placebo in a total of 384 patients of whom 366 were evaluable for effectiveness. Healing, defined as complete re-epithelization of the ulcer site regardless of the persistence or emergence of duodenitis and/or erosions, was evaluated at 2, 4 and 8 weeks, depending on the interval at which the ulcer was found to be healed.

The incidence of healing was highly significantly better than placebo with all doses at all treatment weeks (p 0.001). With the doses of 40 mg h.s., 20 mg b.i.d, 40 mg b.i.d. and placebo, the crude incidence of healing of ulcer was 83%, 82%, 82% and 45% respectively. The respective percentages as calculated by life-table analysis were 88%, 89%, 89% and 55%.

The drug groups showed significant reduction in day and night pain compared to placebo (p 0.001) and in the consumption of antacids. However, the differences between famotidine and placebo in the amount of antacid consumed and the number of days antacid were taken was not clinically significant.

The most common clinical adverse experiences were headache (5.2%) and constipation (3.1%) in the group receiving 40 mg h.s. as contrasted with respective incidences of 11.0% and 1.0% in the placebo group. Eight of 284 patients (3%) receiving famotidine and 5 of the 100 receiving placebo (5%) were withdrawn because of clinical adverse experiences.

Serious clinical adverse experiences reported during the study were either complications of pre-existing conditions or were the result of treatment failure. Serious laboratory adverse experiences were no more frequent in the famotidine groups than in the placebo group.

Based on the results of this study the sponsor recommends a 40 mg h.s. dosage regimen for the short-term therapy of duodenal ulcer.

2. Protocol number: none assigned

a. Title of study: famotidine in the prevention of recurrence of duodenal ulcer.

b. Design of study: double-blind, randomized, multi-center, placebo-controlled dose-ranging study. Patients who had a healed ulcer in the short-term treatment period were invited to enter this (maintenance) phase of the study. The patients were re-randomized to treatment with either famotidine 40 or 20 mg h.s. or placebo. Patients were re-endoscoped after 4 weeks (up to 42 days on treatment), 12 weeks (days 43-105) and 24 weeks (day 106 and later), unless symptomatic relapse called for endoscopic examination before the scheduled return visit.

c. Investigators: twenty-four of the 34 investigators who participated in the short-term trial participated in this trial. Fifteen of the investigators contributed 5 or fewer patients, while only 7 contributed 10 or more. The success of the investigators in enrolling eligible patients into the long-term trial varied over a considerable range from 55 to 88%.

d. Results

(1) Comparability of the patient groups: 54 patients were allocated to 40 mg h.s., 57 to 20 mg h.s. and 65 to placebo. The treatment groups were comparable in all essential respects (table 18).

TABLE 18

Comparability of Treatment Groups

	FAMOTIDINE 40 HS (N=54)	FAMOTIDINE 20 HS (N=57)	PLACEBO (N=66)
Age (Years), Mean	50.6**	46.6	43.3
Sex			
Females	14 (26%)	15 (26%)	17 (26%)
Males	40 (74%)	42 (74%)	49 (74%)
Treatment in Acute Study			
Famotidine 40 HS	14 (26%)	18 (32%)	17 (26%)
Famotidine 20 BID	16 (30%)	15 (26%)	12 (18%)
Famotidine 40 BID	15 (28%)	16 (28%)	22 (33%)
Placebo	9 (17%)	7 (12%)	15 (23%)
Week Ulcer Healed in Acute Study			
Week 2	29 (54%)[a]	26 (46%)	25 (38%)
Week 4	20 (37%)	20 (35%)	31 (47%)
Week 8 or Later	5 (9%)	11 (19%)	10 (15%)
Smoking	31 (57%)	40 (70%)	42 (64%)
Drinking	12 (22%)	8 (14%)	14 (21%)
Initial Ulcer Size, Mean	0.82	0.89	0.92
Number of Ulcers			
One	42 (78%)	49 (86%)	60 (91%)
Two or More	12 (22%)	8 (14%)	6 (9%)
Age at First Ulcer (Years), Mean	43.5*,+	37.7	36.1
Duration of Ulcer Disease (Years), Mean	7.0	8.8	7.3
Ulcer History			
None	25 (46%)	21 (37%)	21 (32%)
One Previous Episode	17 (31%)	22 (39%)	24 (36%)
Multiple Previous Episodes	12 (22%)	14 (25%)	21 (32%)
Other Pathology in Esophagus	13 (25%)	13 (23%)	19 (29%)
Other Pathology in Stomach	13 (25%)[b]	7 (12%)	9 (14%)
Other Pathology in Duodenum	30 (57%)	30 (53%)	30 (45%)

*,** Significantly different from placebo group, $p<0.05$, $p<0.01$ respectively.
+ Significantly different from famotidine 20 HS group, $p<0.05$.
a,b Different from Placebo group, $p=0.08$, $p=0.10$ respectively.

(2) Exclusions from analysis for effectiveness (table 19): the most frequent reason for exclusion was failure to take the prescribed medication for various periods of time at various intervals of the trial. The proportion of patients excluded from the analysis for effectiveness of 40 mg h.s., 20 mg h.s. and placebo was respectively 9%, 14% and 6% which is not a bad record for a 6 month trial. In addition to these exclusions a number of patients dropped out at at various intervals during the trial for various reasons; the sponsor's accounting for these patients is a matter to be addressed by our biometricians.

TABLE 19

Exclusions from Analysis of Effectiveness

	Treatment 40 HS N = 54	20 HS N = 57	PLA N = 66
Off drug[a]	3	4	4
Off drug[b]	1	2	0
Off drug[c]	0	1	0
Protocol deviation	1	1	0
Total	5 (9%)	8 (14%)	4 (6%)
Included in analysis for effectiveness	49	49	62

[a] More than 7 consecutive days
[b] More than 5 days during weeks 1-4
[c] More than 10 days during weeks 5-12

(3) Safety

(a) Vital signs (table 20): the only statistically significant change from baseline was an increase in mean systolic BP from 121.7 to 126.1 in patients receiving 20 mg h.s. It is doubtful whether this has any clinical importance.

TABLE 20

Effect of Treatment on Vital Signs, Mean Values

Measurement	Treatment Group	N	Baseline	Endpoint	Change From Baseline
Body Weight (lbs)	Famotidine 40 HS	15	174.0	172.3	-1.7
	Famotidine 20 HS	11	171.6	172.3	0.6
	Placebo	34	168.0	168.3	0.2
Pulse (beats/min)	Famotidine 40 HS	54	71.7	72.0	0.2
	Famotidine 20 HS	52	74.6	73.5	-1.1
	Placebo	64	72.9	75.8	2.9[B]
Systolic Blood Pressure (mmHg)	Famotidine 40 HS	54	121.6	122.2	0.6
	Famotidine 20 HS	52	121.7	126.1	4.4*,+
	Placebo	65	123.3	120.9	-2.4
Diastolic Blood Pressure (mmHg)	Famotidine 40 HS	54	76.5	76.1	-0.4
	Famotidine 20 HS	52	79.1	79.4	0.3
	Placebo	65	76.3	77.6	1.3

* Significantly different from placebo group, $p < .05$.
\+ Significant change from baseline, $p < .05$.
B Change from baseline, $0.05 \leq p \leq 0.10$.

(b) Clinical adverse experiences: the incidence of adverse signs/symptoms was similar in the 3 groups (40 h.s. 23%, placebo 29%). The number withdrawn because of adverse experiences was no greater with famotidine (4/111, 4%) than with placebo (6/66, 10%).

Adverse clinical experiences classified by body system (table 21) or by symptoms (table 22) were generally no more frequent in patients receiving famotidine than in those receiving placebo.

TABLE 21

Clinical Adverse Experiences

Body System	Famotidine 20 MG (N = 57)	Famotidine 40 MG (N = 64)	Placebo (N=66)
Body as a whole	0	2 (3.1%)	1 (1.5%)
Central nervous	5 (8.8%)	6 (11.1%)	7 (10.5%)
Cardiovascular	0	1 (1.9%)	0
Digestive	6 (10.5%)	7 (13.0%)	11 (16.7%)
Respiratory	3 (5.3%)	3 (5.6%)	5 (7.6%)
Tegumentary	2 (3.5%)	1 (1.9%)	3 (4.5%)
Musculoskeletal	4 (7.0%)	2 (3.7%)	1 (1.5%)
Special Senses	1 (1.8%)	1 (1.9%)	1 (1.5%)
Urogenital	1 (1.8%)	2	0

TABLE 22

Clinical Adverse Experiences with 12% Incidence

	Famotidine 20 MG N = 57	Famotidine 40 MG N = 64	Placebo N = 66
Abdominal Pain	3 (5.3%)	3 (5.6%)	4 (6.1%)
Headache	2 (3.5%)	4 (7.4%)	4 (6.1%)
Constipation	2 (3.5%)	1 (1.9%)	2 (3.0%)
Back Pain	2 (3.5%)	1 (1.9%)	0
Pruritis	2 (3.5%)	0	0
Constipation	1 (1.8%)	2 (3.7%)	1 (1.5%)
Paresthesia	1 (1.8%)	2 (3.7%)	0

(-) Serious clinical adverse experience were reported in 3 patients:

A 59 year old male with hypertension and atherosclerosis receiving famotidine 40 mg h.s. was admitted to the hospital on day 69 with a 2-week history of a severe right-sided head and face pain with 3 to 4 episodes of transient blindness in the right eye. A CT scan demonstrated a recent infarct in the distribution of the right middle cerebral artery. Angiography showed complete occlusion of the right, and partial occlusion of the left internal carotid. Therapy with famotidine was discontinued. The investigator considered this experience not drug-related.

A 50 year old male with a prior history of hemoptysis was receiving famotidine 40 mg h.s. when a diagnosis of pulmonary tuberculosis was made and the drug was discontinued on study day 36. The investigator believed the experience was definitely not related to drug therapy.

A 61 year old female with chronic obstructive pulmonary disease was admitted to the hospital with non-specific chest pains of 2 days duration after 42 days on placebo. The patient has been lost to follow-up. The investigator considered the experience definitely not drug-related.

(d) Laboratory adverse events were not serious and were no more frequent in the famotidine-treated patients than in the placebo-treated patients (table 23). There were 2 withdrawals from the trial in the famotidine group, one in the placebo group because of adverse laboratory events, but a drug-relationship was extremely doubtful in all cases.

TABLE 23

Laboratory Adverse Events/Number at Risk

	Famotidine 20 MG N=57	Famotidine 40 MG N=64	Placebo N=66
Hematology	3/52	5/54	1/64
Renal Function	0/51	3/53	0/64
Liver Function	11/51	3/53	13/64
Metabolic	3/51	0/54	0/60
Urogenital	3/51	6/34	9/60

(4) Effectiveness

(a) Incidence of recurrence: the sponsor's tabulation divides the duration of treatment into 3 periods, days 1-42, 43-105 and 106 or later (table 24). By life-table analysis it is clear that the incidence of recurrence with placebo (67%) is statistically significantly higher at the end of the 6 month trial than that with famotidine 40 mg h.s. (31%) and 20 mg h.s. (26%). However, because of the wide spread of the intervals allowed for the respective periods (e.g., period 3, the 6-month interval, includes endoscopies performed from day 106 onward) an endoscopic finding at 15 or 16 weeks would be included in the 24 week analysis. To get some conception of the rate as well as the incidence of recurrence, I requested the sponsor to prepare a tabulation showing the numbers for each 4-week period (table 25). From these data it is clear that, as has been shown in

TABLE 24

Cumulative Percent Recurrence, Life-Table Analysis

	40 mg	20 mg	PLACEBO	p
Period 1 (days 1-42)	6	1.8	12.1	40 vs 20: <0.01; 20 vs PLA: <0.05
Period 2 (days 43-105)	15.2	17.8	51.4	40 vs 20: <0.01; 20 vs PLA: <0.01
Period 3 (days 106 or later)	30.8	25.5	66.7	40 vs 20: <0.01; 20 vs PLA: <0.01

TABLE 25

Number of Patients who Relapsed (%)* (Life Table Data)

	FAMOTIDINE 40 mg (N=56)	FAMOTIDINE 20 mg (N=57)	PLACEBO (N=66)
Month 1 (Days 1-28)	0 (0)	0 (0)	3 (5)
Month 2 (Days 29-56)	1 (2)	1 (2)	10 (16)
Month 3 (Days 57-84)	2 (4)	1 (2)	13 (22)
Month 4 (Days 85-112)	8 (15)	9 (18)	30 (54)
Month 5 (Days 113-140)	8 (19)	10 (23)	33 (62)
Month 6 (Days 141-168)	8 (19)	10 (21)	36 (64)
After Month 6 (Days 169-231)	11 (32)	12 (28)	38 (67)

*All Patients Treated Analysis

previous trials of prevention of recurrence, the recurrences tend to occur within the first 4 months. The bottom line, however, remains the same, in that the data provide evidence of effectiveness of famotidine in both dosages in reducing the incidence of recurrence of duodenal ulcer.

(b) Antacid consumption: the percent of patients taking antacids during the trial was the same on famotidine 40 h.s. (12%), 20 h.s. (14%) and placebo (15%).

e. Summary: 177 of the patients whose duodenal ulcers had healed in the short-term trial were admitted to a one year trial of famotidine, 40 mg h.s., 20 mg h.s. or placebo in the prevention of recurrence. At the time of this submission data were insufficient to report on the results beyond 6 months. The limited achievement of short-term healing is illustrated by the 67% incidence of recurrence in 6 months in patients receiving placebo. Both doses of famotidine reduced the incidence by about the same order of magnitude; the sponsor's recommended "maintenance" dose, 20 mg h.s., yielded a 25% incidence of recurrence. In this trial the drug was safe; clinical and laboratory adverse experiences were no more frequent in patients receiving the drug than in those receiving placebo.

f. Comment: bringing about healing of the duodenal ulcer in the short-term is no great clinical problem; it can be achieved as well with a few daily doses of antacid as with any of the systemically acting drugs. The problem in peptic ulcer disease is to prevent recurrence and thereby avoid intractability. Famotidine is clearly superior to placebo in this respect

but the 21% incidence of recurrence within 6 months with the recommended dose of 20 mg h.s. still leaves quite a bit to be desired. To compare the effectiveness of famotidine with that reported for other drugs it will be necessary to await the completion of the 1-year trial.

A single bedtime dose would have a cost-effective advantage, but as for the contention that it improves compliance, I doubt that patients would be any less compliant with a regimen of one tablet in the morning and one tablet in the evening. Since it may be possible to achieve even greater effectiveness in the prevention of recurrence than was obtained in this trial, the sponsor should consider a trial of a dose of 40 mg b.i.d., or perhaps 40 mg in the morning and 20 mg in the evening.

3. Study No. 41

a. Title: An open-label study to evaluate the use of famotidine in patients with peptic ulcer, Zollinger-Ellison Syndrome resistant to or intolerant of cimetidine or ranitidine or both.

b. Design of study: Open-label, uncontrolled study.

c. Investigator: Sidney Cohen, M.D., Hospital of the University of Pennsylvania, Philadelphia, PA.

d. Results (table 26)

(1) Characteristics of patients entered into the study: the basal acid output in the first 3 patients in the table is surprisingly low, especially in the face of the elevated serum gastrins.

(2) Safety: two of the patients had adverse effects, both requiring discontinuation from the study. One patient had severe abdominal pain, the other elevated liver enzymes which, however, were not clearly attributable to famotidine since the patient had had multiple blood transfusions and the enzymes were slightly elevated prior to entry into the study.

(3) Effectiveness: famotidine controlled the symptoms in all patients on doses titrated to the individual patient; doses as high as 400 mg/day were required. Three patients had been receiving famotidine for approximately one year at the time of this report (January 25, 1984).

e. Summary: a satisfactory response to therapy was achieved in 7 patients with possible or proven Z-E syndrome who had not been adequately controlled or had had adverse effects on cimetidine or ranitidine.

f. Conclusions: famotidine was usually well tolerated in patients with Z-E syndrome and may be useful in patients resistant to or intolerant of other H_2-blockers.

TABLE 26

Zollinger-Ellison Patients Treated With Famotidine

Patient No.	Age	Sex	BAO mEq/hr.*	MAO** mEq/hr.	Gastrin pg/ml	Diagnosis	Concomitant Conditions	Previous Therapy	Reason Previous Therapy Discont.	Final Dosage mg	Duration in Study	Adverse Events
1	64	M	1.8	19.3	298	Probable Z-E	sick sinus syndrome, asthma	Cimetidine	Serum Creatinine Gynecomastia	80 BID	1 yr.	
2	46	M	10.2+	-	461	Z-E	PEA, hypothyroidism,	Cimetidine Ranitidine	Recurrent Ulcer on Cimetidine	160 AM 160 PM	1 yr.	
3	63	F	7.5	-	500	Z-E	None	Cimetidine Ranitidine	Decreased effective ness on cimetidine Recurrent ulceration on ranitidine	20 BID	1 yr.	
4	43	M	75	90	1702	Z-E	Hypertension	Cimetidine Ranitidine	Severe abdominal pain	0/0	1 day	Severe abdominal pain discontinued from study
5	29	M	37.7	95.3	391	Z-E	None	Cimetidine Ranitidine	Recurrent pain and ulcer on cimetidine	60 BID	5 wks.	
6	47	M	6.5 (Tumor Metastatic)			Z-E	None	Cimetidine Ranitidine	CNS side effect Recurrent anastomotic ulcers on cimetidine	160 BID	2 mo.	Liver enzymes elevated, discontinued from study.
7	52	F	61.0		476	Z-E	COPD anxiety hiver	Cimetidine Ranitidine	Decreased effectiveness on cimetidine	60 BID	1 mo.	

*BAO-Basal acid output per hour, **MAO Maximal acid out per hour, +Obtained in 1981.

4. Study No. 6

a. Title of study: the use of famotidine in patients with hypersecretion of acid.

b. Investigator: Robert T. Jensen, M.D., Digestive Disease Branch, NIH, Bethesda, MD.

c. Design of study: open study divided into an acute phase and a long-term phase. The acute phase was conducted to compare the potency, onset of action, and duration of action of famotidine with cimetidine and ranitidine. A non-randomized block design was used.

Patients included in the study met the criteria of Zollinger-Ellison syndrome defined by a basal gastric acid output greater than 15 mEq/hr, a fasting serum gastrin concentration of greater than 100 pg/ml (normal less than 100 pg/ml), and a rise in the serum gastrin concentration of greater than 200 pg/ml after intravenous infusion of 2 units/kg of secretin. Patients under 18 years of age or women capable of becoming pregnant were excluded.

The critical evaluation criterion in this study was the level of hourly gastric acid output. An effective dose was defined as that which maintained the gastric acid secretion below 10 mEq/hour in the sixth hour following a dose.

At the start of the study, H_2-blockers were discontinued and gastric acid secretion was followed until it rose abcve 10mEq/hour. At that time, famotidine 20 to 60 mg was given every six hours for at least 4 doses. Selection of the starting dose of famotidine was based on the patient's response to previous treatment with H_2-blockers. Famotidine dosage was adjusted by 20 mg increments every 6 hours until the gastric acid output during the sixth hour post-drug was below 10 mEq. This dose was continued through the next day and gastric secretion measured again to ensure suppression of gastric acid to below 10mEq/hour.

The minimum 6-hourly doses of cimetidine and ranitidine were determined similarly; the adjustment increment of cimetidine was 300 mg, of ranitidine 150 mg, every 6 hours.

If doses of more than 160 mg of famotidine, 1500 mg of ranitidine, or 3,600 mg of cimetidine were required every 6 hours, the patient was defined as resistant to the respective drug and an anticholinergic, isopropamide 5 mg, was given every 6 hours in addition to the H_2-blocker. The minimum 6-hourly dose requirements were then determined as described above. The minimum doses of each drug that reduced gastric acid secretion to the same degree (to below 10 mEq/hr during the sixth hour after a dose) were considered equipotent.

In the long-term phase patients were treated continuously with famotidine alone for up to 38 weeks to investigate the safety, tolerability and required adjustments of the famotidine maintenance dose. They were evaluated at two weeks, two months and thereafter at two monthly intervals after beginning famotidine therapy. The initial dose was the minimum dose identified in the short-term study. Dosage was titrated as needed to ensure continued suppression of gastric acid below 10 mEq/hour.

d. Results

(1) Characteristics of patients studied (table 27): 11 patients were evaluated. It is obvious that they were all sick people.

TABLE 27

Characteristics of Patients Treated With Famotidine

Pt. No.	Age	Sex	Disease Duration (Yrs.)	Tumor Status	Prior Antisecretory Therapy	Basal Acid Output (mEq/hr)	Gastrin Basal (pg/ml)	Secondary Diagnoses
1	60	M	3	None	Ranitidine 300BID	55.6	100	Peripheral vascular disease, chest pain.
2	61	F	7	Suspected	Cimetidine	40.1	6,100	Liver mal., obesity, diabetes, low back pain.
3	55	M	1	None	Ranitidine	20.6	87 94	Myocardial infarction, borderline diabetes, chronic bronchitis.
4	50	M	7	Proven*	Ranitidine	44.6	19-30,000	Diabetes, Gilbert's Syndrome.
5	65	M	6	Suspected	Ranitidine	35.0	1,700	Cancer of prostate, hypertension.
6	22	M	2	Proven*	Ranitidine 300BID	44.6	520-590	Deep vein thrombosis.
7	60	F	5	None	Cimetidine 800BID	24.0	430	Obesity menorrhagia.
8	50	M	15	None	Cimetidine 800BID	100.3	3,000	Multiple sclerosis, barrett's esophagus, colon polyps, alcohol liver disease.
9	47	F	2	Proven*	Cimetidine	10.1	7,000	Obesity, hyperthyroidism, idiopathic cystic edema.
10	58	M	7	Suspected	Ranitidine 300BID	50.0	4,200	Hyperthyroidism, L adrenal mass, prostatic hypertrophy
11	66	M	7	None*	Ranitidine	30.2	615	mild chronic renal failure, alcoholic induced fatty liver; upper motor neuron disorder.
Mean						44.2	4,091	

*Laparotomy performed, **Pancreatic tail lesion resected.

(a) Clinical adverse experiences: possibly drug-related symptoms prompted discontinuation of famotidine in 2 patients. Pre-existing alopecia in a woman worsened after 80 days; intermittent fever occurred in a male patient on famotidine for 252 days.

(b) Laboratory adverse events: famotidine was discontinued in 2 patients, one after 160 days with increased SGPT which was present at the outset and one after 241 days with marginal eosinophilia, elevated ESR and leukopenia.

(2) Effectiveness

(a) Relative potency of famotidine vs cimetidine and ranitidine: famotidine averaged 34 times as potent as cimetidine (range 15-75), 9 times as potent as ranitidine (range 2.5-15).

(b) Onset of action (figure 37): there was no difference among the 3 drugs in the rate of onset of action.

(c) Duration of action (figure 38): mean hourly gastric acid output remained below 10 mEq for 8 hours post-famotidine administration while the mean acid output at that interval was about 12 mEq with both cimetidine and ranitidine, not an impressive difference. From the 10th to 12th hours, however, acid was more effectively suppressed with famotidine than with either of the other drugs.

Figure 38
Duration of Action of Famotidine, Cimetidine, and Ranitidine

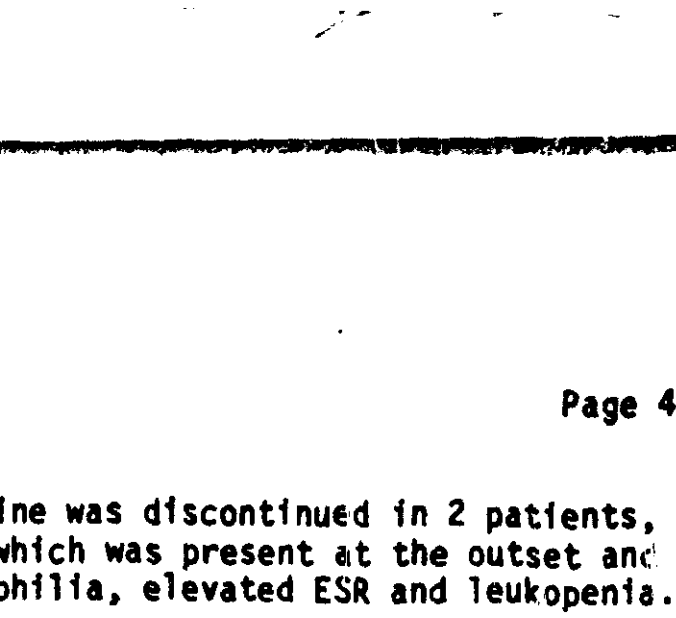
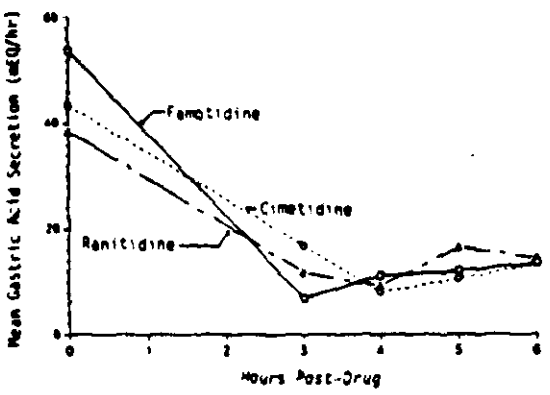


Figure 37
Onset of Action of Famotidine Compared With Cimetidine and Ranitidine (N = 6)



e. Summary: The summary and conclusions are set forth succinctly in the published paper by Howard et al (Gastroenterology 1985; 88:1026-1033, reprint attached). Famotidine was similar to the two other H_2-blockers in that equipotent doses had the same onset of action, time to maximum activity, patient tolerance, lack of evidence of hepatotoxicity and hematotoxicity, requirement for periodic adjustment of dose, and correlation among individual daily doses required to control gastric secretion. Famotidine differed from the other two drugs in that it had a longer duration of action, possibly attributable to a longer occupation of the H_2-receptor site,which, however, does not necessarily result in a less frequent dosing interval. Famotidine differed from cimetidine in that long-term high-dose treatment in males was not associated with anti-androgen side effects.

B. Foreign clinical trials

1. Study No. 5006

a. Title of study: 'A double-blind study in out patients to compare famotidine with ranitidine in the short-term treatment of duodenal ulceration.

b. Design of study: the protocol for this trial was identical to that outlined for the U.S. multicenter trial except that (1) instead of placebo, the reference control treatment was ranitidine 150 mg b.i.d, and (2) scores for severity of pain and of other symptoms were defined:

(1) Day pain

0 none
1 mild = bothered a little; pain is present part of the day, but causes little or no discomfort.
2 moderate = bothered to some degree; pain is present most of the day, annoying, but not interfering with daily routine.
3 severe = bothered intensely; constant pain causing marked interference with daily routine.

(2) Night pain

0 none
1 mild = bothered a little; pain is present part of the night, but does not interfere with sleep.
2 moderate = bothered to some degree; pain is present most of the night, occasionally interferes with sleep.
3 severe = bothered intensely; constant pain, marked interference with sleep.

(3) Other symptoms

(a) abdominal discomfort
(b) feeling of fullness
(c) flatulence
(d) acid regurgitation
(e) heartburn
(f) nausea
(g) vomiting
(h) other

(4) Severity of these symptoms was scored as follows:

0 none
1 mild = awareness of sign or symptom, but easily tolerated.
2 moderate = discomfort enough to cause interference with usual activity.
3 severe = incapacitating with inability to work or carry out usual activity.

(5) Global response to therapy was assessed by the patient as follows:

4 excellent = best possible anticipated response; abdominal pain completely relieved, other symptoms improved or no worse than usual.

3 good = good response; abdominal pain almost completely relieved, other symptoms improved or no worse than usual.

2 fair = definite response, but could be better; some relief of abdominal pain, other symptoms unchanged or worse.

1 poor = minimal response; little or no relief of abdominal pain, other symptoms unchanged or worse.

0 none = no response, absence of drug affect.

(5) The dosage schedule was as follows (all doses in milligrams):

Treatment Group	8:00 AM	10:00 PM
Famotidine 40 h.s.	placebo famotidine placebo ranitidine	famotidine 40 placebo ranitidine
Famotidine 20 b.i.d.	famotidine 20 placebo ranitidine	famotidine 20 placebo ranitidine
Famotidine 40 b.i.d.	famotidine 40 placebo ranitidine	famotidine 40 placebo ranitidine
Ranitidine 150 b.i.d.	placebo famotidine ranitidine 150	placebo famotidine ranitidine 150

c. Investigators (table 28): 68 investigators in 19 countries, all qualified by training and experience to conduct clinical trials, participated in this study.

d. Results

(1) Comparability of treatment groups (table 29): the number of patients in the respective groups were famotidine 40 h.s. 255, 20 b.i.d. 259, 40 b.i.d. 258, ranitidine 150 b.i.d. 259. The four treatment groups were essentially comparable in numbrs and in all other respects. There was no significant difference in the mean age between males and females.

TABLE 29

Comparability of Treatment Groups

	FAMOTIDINE 40 HS (n=255)	FAMOTIDINE 20 BID (n=259)	FAMOTIDINE 40 BID (n=258)	RANITIDINE 150 BID (n=259)
Age (Years), Mean	42.5	40.1	43.1	45.4
Sex				
Males	171 (66%)	173 (67%)	166 (74%)*	198 (77%)*
Females	79 (31%)	86 (33%)	63 (24%)	84 (32%)
Weight (Kg)	66.5	68.6	68.8	69.3
Smoking	156 (61%)	150 (58%)	160 (62%)	148 (57%)
Alcohol	120 (50%)	121 (47%)	114 (44%)	121 (47%)
Initial Ulcer Diameter, Mean	0.85	0.91	0.96	0.91
Number of Ulcers				
One (90%)	235 (88%)	230 (99%)	230 (99%)	232
Two or More	30 (12%)	29 (11%)	28 (11%)	26 (10%)
Age at First Ulcer(Years), Mean	38.6	38.0	37.7	38.9
Duration of Ulcer Disease (Years), Mean	5.1	5.8	5.4	6.6
Ulcer History				
None	75 (29%)	77 (30%)	75 (31%)	71 (27%)
One Previous Episode	73 (28%)	75 (29%)	67 (28%)	62 (24%)
Multiple Previous Episode	109 (42%)	117 (45%)	112 (47%)	126 (49%)
Other Pathology in Esophagus	25 (10%)	32 (12%)	32 (13%)	31 (12%)
Other Pathology in Stomach	51 (20%)	50 (19%)	54 (23%)	64 (25%)
Other Pathology in Duodenum	113 (44%)	108 (42%)	121 (47%)	117 (45%)
Concomitant Conditions				
Anemia	6 (2.4%)	1 (0.4%)	0	0
Anxiety disorders	2 (0.8%)	4 (1.5%)	4 (1.6%)	8 (3.1%)
Asthma	1 (0.4%)	1 (0.4%)	6 (2.3%)	4 (1.5%)
Cholecystectomy	5 (2.0%)	10 (3.9%)	7 (2.7%)	4 (1.5%)
Hypertension	13 (5.1%)	16 (6.2%)	10 (3.9%)	14 (5.4%)
Insomnia	5 (2.0%)	3 (1.2%)	0	1 (0.4%)

*Significantly different from the famotidine 20 BID group (p<0.05).
For patients with more than one ulcer, this was the size of the largest ulcer.
One patient did not have a duodenal ulcer.
n=255, n=257, n=258

Table 28

Argentina		
De Vecchi, A.G.F.	Director of the Hospital	Ramos Mejia Hospital, Buenos Aires
Kohan, S.	Chief of Gastroenterology	Pirovano Hospital, Buenos Aires
Segal, J.E.	Chief of Gastroenterology	Durand Hospital, Buenos Aires
Australia		
Coulston, K.J.	Specialist in Gastroenterology	Concord General Hospital, Sydney
Mansky, J.	Gastroenterologist	Prince Henry's Hospital, Melbourne
Piper, D.W.	Visiting Medical Officer	Royal North Shore Hospital, St. Leonards
Shearman, J.C.	Chairman, Dept. of Medicine	Royal Adelaide Hospital, Adelaide
Austria		
Mentschel, E.	Internist	Hanusch Hospital, Vienna
Reichel, W.	Director of Endoscopical	Wilhelminen Hospital, Vienna
Schütze, K.	Specialist in Internal Medicine	Hanusch Hospital, Vienna
Brazil		
Battarello, A.	Professor	Medical School of Sao Paulo
Castro L.	Gastroenterologist	Federal University of Minas Gerais, Belo Horizonte
Canada		
Archambault, A.	Head of Gastroenterology	Maisonneuve-Rosemont Hosp., Montreal
Hunt, R. H.	Head of Gastroenterology	McMaster U. Med. Cent. Hamilton
Marcon, N.E.	Head of Gastroenterology	The Wellesley Hospital, Toronto
Colombia		
Aponte, L.	Endoscopist/Gastroenterologist	Carrera 18 No. 80-67, Bogota
Denmark		
Kehlet, H.	Head Surgeon	Arhus Council Hospital, Arhus
England		
Brown, P.	Consultant Physician	Royal Shrewsbury Hosp., Shrewsbury
Cockel, R.	Consultant Physician	Sally Oak Hospital, Birmingham
Cowan, R.E.	Consultant Physician	Essex County Hospital, Colchester
Fairclough, P.D.	Consultant Physician	St. Bartholomew's Hospital, London
Garnham, J.C.	Endoscopist	Wexham Park Hospital, Slough
Levi, A.J.	Consultant Gastroenterologist	Northwick Park Hospital, Harrow
Record, C.O.	Consultant Physician	Royal Victoria Infirmary, Newcastle
Vicary, F.R.	Consultant Physician	Whittington Hospital, London
Finland		
Kairiitainen, O.	Chief of Gastroenterology	University Central Hosp. Tampere
Salaspuro, M.P.J.	Chief, Gastroenterology	University Central Hosp. Helsinki
France		
Corayon, P.	Head of Gastroenterology	Centre Hosp. Regional, Besancon
Chaput, J.	Head of Gastroenterology	Hospital Antoine Beclere, Clamart
Ferrier, J.P.	Dept. Head, Gastroenterology	Hospital Jean Verdier, Bondy
Paris, J.C.	Head of Gastroenterology	Centre Hospitalier Regional, Lille
Ribet, A.	Dept. Head, Gastroenterology	U. Hospital of Toulouse-Rangueil
Germany		
Baumann, H.G.	Gastroenterologist	Bethanien Hospital, Hamburg
Jakob, G.	Head, Dept. Gastroenterology	District Hosp. Eichstaett, Eichstaett
Niederer, S.E.	Professor of Gastroenterology	Medical University Poliklinik, Bonn
Ottenjann, R.	Head of Internal Medicine	Municiple Hosp. Mue Memmerlach, Munich
Paul, F.	Head of Medical Clinic II	Klinik Ingolstadt, Ingolstadt/Donau
Scholten, T.	Assistant Professor Gastro-enterology	Med. Klinik u. Poliklinik University, Duesseldorf
Schuetz, E.	Internist/Gastroenterologist	Gastroenterology-Proktology, Regensburg
Seifert, E.	Head of Gastroenterology	Municipal Hospital Kemperhof, Koblenz
Simon, B.	Specialist for Gastroenterology	Medical University Klinik, Heidelburg
Stadelmann, O.	Head of Dept. of Gastro-	Chm d. Medical Klinik II, Fuerth
Holland		
Kettner, M.	Internist	Gasthuis Middelburg, Middelburg
Wesdorp, I.C.E.	Gastroenterologist	Andreas Hospital, Amsterdam
Ireland		
Crowe, J.	Gastroenterologist	Mater Misericordiae Hospital, Dublin
Gleeson, F.	Consultant Physician, Lecturer	James Connolly Memorial Hosp., Dublin
Weir, D.G.	Consultant Gastroenterologist	St. James' Hospital, Dublin
Italy		
Baglioni, A.	Surgeon, Lecturer	Hospital Generale Provinciale
Barbara, L.	Director of Gastroenterology	Hospital Sant'Orsola, Bologna
Bianchi-Porro, G	Director of Gastroenterology	Hospital L Sacco, Milan
Blasi, A.	Director of Gastroenterology	Hospital Vittorio Emanuele II, Catania
Carobbiuta, F.	Head Surgeon	Municipal Hospital of Cassino,
Chelt, A.	Chief Dept. of Gastroenterology	Hospital S. Martino, Genova
Dal Monte, P.R.	Head Gastroenterologist	Hospital Bellaria, Bologna
Francavilla, A.	Head Physician	Cattedra di Malattie Apparato Digerent, Bari
Materazzo, P.F.	Assistant Surgeon	Municipal Hospital of Ferrara,
Mazzacca, G.	Div. of Gastroenterology	School of Medicine, Naples
Paoluzi, P.	Gastroenterologist	II Clinical Medica Universita di Roma
Speranza, V.	Head of Surgical Clinic	VI Clinical Chirurgica University degli Studi di Roma
Toti, F.	Head Surgeon	Municipal Hospital of Subiaco
Vagni, V.	Consultant Endoscopist	Municipal Hospital, Castellana
Verme, G.	Head Physician	Hospital Molinette, Torino
Mexico		
Villalobos, J.	Head of Dept. of Gastroenterogy	National Institute of Nutrition, Mexico, D.F.
New Zealand		
Tasman-Jones, C.	Associate Professor	Auckland Med. School, Auckland
Norway		
Fausa, O.	Head of Dept. of Gastro-enterology	Riks Hospital, Oslo
South Africa		
Dentlewitz, M.D.	Head, Medical Gastroenterology	Johannesburg Hosp., Parktown
Marks, I.N.	Head, Gastrointestinal Clinic	Groote Schuur Hospital,
Sweden		
Hradsky, M.	Chief of Gastroenterology Unit	Falu Hospital, Falun

(2) Exclusions from analysis of effectiveness: the number of patients excluded from analysis of healing because of protocol violations (table 30) was gratifyingly small, amounting to a total of 5%. Even the numbers lost from analysis because of absence of data on pain and global response (table 31) left a sufficiently large data base for meaningful analysis.

TABLE 30

Exclusions from Analysis of Effectiveness

Protocol Violation	Famotidine 40 HS	Famotidine 20 BID	Famotidine 40 BID	Ranitidine 150 BID	Total
Concomitant Drug	7	2	5	5	19
Initial Endoscopy or Ulcer Size Out of Range	5	6	3	4	18
Prior Surgery	1	0	1	0	2
Uncooperative Patient	2	4	2	4	12
TOTAL	15	12	11	13	61

TABLE 31

Number of Patients Omitted From Analysis of Effectiveness

	Famotidine 40 HS N=255			Famotidine 20 BID N=259			Famotidine 40 BID N=250			Ranitidine 150 BID N=259		
	WK 2	WK 4	WK 8	WK 2	WK 4	WK 8	WK 2	WK 4	WK 8	WK 2	WK 4	WK 8
Protocol Violators	15	15	15	12	12	12	11	11	11	13	13	13
No Day/Night Pain Data	25	21	20	20	17	20	18	17	18	21	19	19
No Global Response Data	44	23	23	37	16	17	39	18	18	40	18	18
NUMBER EVALUABLE												
Ulcer Healing	240	240	240	247	247	247	247	247	247	246	246	246
Day/Night Pain	230	234	235	239	242	239	240	241	240	238	240	240
Global Response	211	232	232	222	243	242	219	240	240	219	241	241

(3) Safety

(a) Vital signs (table 32): changes during treatment from baseline value were statistically significant for some or all of the treatments, but none of the changes were of clinical concern.

TABLE 32

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE	COMMENTS
Weight (kg)	40 HS	244	68.5	68.8	0.3	Increase for
	20 BID	252	69.6	69.8	0.2	each treatment
	40 BID	247	69.8	70.0	0.2	(p 0.01)
	Ranit	249	69.3	69.7	0.4	
Pulse	40 HS	239	75.0	74.0	-1.0	40 BID lower
	20 BID	248	75.2	74.6	-0.6	than 40 HS
	40 BID	240	73.6	73.4	-0.2	and 20 BID
	Ranit	242	74.4	74.0	-0.4	(p 0.5)
Systolic BP (mmHg)	40 HS	238	126.0	124.7	-1.3	No
	20 BID	249	126.9	126.5	-0.4	significant
	40 BID	241	126.1	125.6	-0.5	differences
	Ranit	244	129.9	125.7	-1.2	
Diastolic BP (mmHg)	40 HS	238	79.6	78.5	-1.1	40 HS and
	20 BID	249	79.6	79.1	-0.5	40 BID
	40 BID	241	79.6	78.6	-1.0	decreased
	Ranit	243	79.3	78.7	-0.6	p 0.05

(b) Clinical adverse events: adverse symptoms occurring with an incidence of 1.5% or more in at least one of the treatment groups (table 33) were primarily in the central nervous system (CNS) (famotidine 6%, ranitidine 8%) and the gastrointestinal (GI) system (famotidine 4%, ranitidine 5%). The most common CNS symptom, headache, occurred in 4% on both famotidine and ranitidine. The incidence of the most common GI symptom, diarrhea, was 1.3% on famotidine, 1.9% on ranitidine. The adverse experiences were considered serious in only 2/772 (0.2%) of patients receiving famotidine, 3/259 (1.2%) of those receiving ranitidine. Very few of the adverse symptoms were drug-related; e.g. the incidence of withdrawal of patients because of adverse experiences (table 34) was very low. Moreover such events as hemorrhage, development of a gastric ulcer or perforation of a duodenal ulcer are more appropriately classified as failures of therapy than as adverse drug effects.

TABLE 33

Clinical Adverse Experiences by Body System (%)

	Famotidine 40 MS (N=256)	Famotidine 20 BID (N=256)	Famotidine 40 BID (N=256)	Ranitidine 150 BID (N=258)
Body as a Whole	5 (2.0)	7 (2.7)	6 (1.6)	5 (1.9)
Cardiovascular	3 (1.2)	5	1 (0.4)	0
Digestive	10 (3.9)	12 (4.6)	11 (4.3)	12 (4.6)
Hemic/Lymphatic	0	0	0	1 (0.4)
Metabolism	1 (0.4)	0	0	0
Musculoskeletal	2 (0.8)	3 (1.2)	2 (0.8)	0
Nervous/Psychiatric	12 (5.1)	12 (5.0)	20 (7.8)	20 (7.7)
Respiratory	3 (1.2)	5 (1.9)	8 (3.1)	3 (1.2)
Tegumentary	4 (1.6)	4 (1.5)	1 (0.4)	5 (1.9)
Special Senses	0	0	0	1 (0.4)
Urogenital	0	1 (0.4)	0	0
Total	41 (16)	46 (17)	47 (18)	47 (18)

TABLE 34

Patients Withdrawn Due To Adverse Experience

TREATMENT GROUP	AN	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	TOTAL POSSIBLY/ PROBABLY
Famotidine 40 MS	172	Abdominal pain	Severe	Probably not[a]	
		Eructation	Severe	Probably not	
	42	Diarrhea	Severe	Possibly	
	542	Headache	Severe	Possibly	
	590	G.I. bleeding	Severe	Definitely not	
	1055	Gastric ulcer	Mild	Probably not	4/255 (1.6%)
Famotidine 20 BID	759	Gastric ulcer	Mild	Probably not	
	1130	Perforated duodenal ulcer	Moderate	Probably not	2/259 (0.7%)
Famotidine 40 BID	368	Pain, generalized	Severe	Possibly	
	465	Anorexia	Severe	Definitely	
		Anxiety	Severe	Definitely	
		Headache	Severe	Definitely	2/258 (0.8%)
Ranitidine 150 BID	52	Lung cancer	Severe	Definitely not	
	147	Diarrhea	Severe	Probably	
	721	Depression	Moderate	Possibly	
		Agitation	Moderate	Possibly	
		Concentration loss	Moderate	Possibly	
		Malaise	Moderate	Possibly	3/259 (1.2%)

[a] "Probably not" = "Possibly yes"

(c) Laboratory adverse events were infrequent (table 35), occurring in approximately 4% of patients in each group. No patient was withdrawn because of an abnormal laboratory finding.

TABLE 35

Laboratory adverse events/number at risk

	Famotidine 40 MS (N=255)	Famotidine 20 BID (N=259)	Famotidine 40 BID (N=258)	Ranitidine 150 BID (N=259)
Hematology	6/235	5/242	6/231	3/236
Liver Function	2/229	3/230	3/230	5/234
Renal Function	0/143	0/150	1/140	1/142
Metabolic	0/100	0/104	1/95	0/99
Urogenital	1/236	0/242	2/231	1/236

(4) Effectiveness

(a) Incidence of healing: the sponsor displays the data for incidence of healing at 2, 4, and 8 weeks in the conventional manner (table 36) in which the 2-week endoscopy could be as late as 18 days, the 4-week endoscopy as late as 34 days, and the 8-week endoscopy as late 64 days. The resulting numbers do not correctly reflect the interval of healing, as illustrated by the tabulation in which the incidence of healing is displayed by actual weeks (table 37). As in the U.S. trial, it is clear that the optimal interval to endoscope patients on treatment is 5 weeks. By both methods of calculation, the 20 mg b.i.d. and 40 mg b.i.d. doses of famotidine are more effective at 2, 4 and 8 weeks than the sponsor's proposed dose of 40 mg h.s.

TABLE 36

Cumulative Number Healed/Number Evaluable (%)

Weeks (Day Range) on Treatment	Famotidine 40 mg h.s. N=240	Famotidine 20 mg b.i.d. N=247	Famotidine 40 mg b.i.d. N=247	Ranitidine 150 mg b.i.d. N=246
2 (Days 1-18)	82 (34)	94 (38)	109 (44)	96 (39)
4 (Days 19-34)	164 (68)	191 (77)*	201 (81)*	186 (76)
8 (Days 35-64)	210 (88)	228 (92)	227 (92)	222 (90)
Beyond Week 8 (Days 65-72)	211 (88)	231 (94)*	231 (94)*	223 (91)

* Significantly higher than famotidine 40 n.s., p<.05.

TABLE 37

Cumulative Number Healed (%)

Weeks (Day Range) on Treatment	Famotidine 40 mg h.s. N=240	Famotidine 20 mg b.i.d. N=247	Famotidine 40 mg b.i.d. N=247	Ranitidine 150 mg b.i.d. N=246
Week 1 (Days 2-8)*	0 (0)	0 (0)	0 (0)	0 (0)
Week 2 (Days 9-15)	62 (26)	72 (29)	84 (34)	72 (29)
Week 3 (Days 16-22)	87 (36)	99 (40)	114 (46)	100 (41)
Week 4 (Days 23-29)	141 (59)	165 (67)	173 (70)	163 (66)
Week 5 (Days 30-36)	169 (70)	194 (79)	203 (82)	191 (78)
Week 6 (Days 37-43)	170 (71)	197 (80)	206 (83)	192 (78)
Week 7 (Days 44-50)	170 (71)	197 (80)	206 (83)	193 (78)
Week 8 (Days 51-57)	186 (78)	211 (85)	219 (89)	207 (84)

* Day 1 was the day of the baseline evaluation. Patients started taking drug at bedtime on day 1. All weekly day ranges start with day 2.

(b) The incidence of healing as reported by those investigators who had at least 20 patients (table 38) shows comparatively little treatment by investigator interaction at the important intervals (weeks 4 and 8) except for those intervals where the investigators had too few patients to make the differences meaningful. It is curious but inexplicible that in the sponsor's proposed dose (40 mg h.s.) for the short-term treatment, the total incidence of healing reported by the investigators with 20 or more patients was much higher (85%) than that of all of the rest of the investigators combined (63%). By whatever method the data are calculated, at week 2 and more importantly at week 4, the incidence of healing is higher with ranitidine b.i.d. than with the sponsor's recommended dose of famotidine 40 mg h.s.

TABLE 38

Incidence of Healing Reported by Investigators with at Least 20 Patients

Number (%) Healed

Investigator	City	Famotidine N	Famotidine 40 mg h.s. wk 2	Famotidine 40 mg h.s. wk 4	Famotidine 40 mg h.s. wk 8	Famotidine 20 mg b.i.d. N	Famotidine 20 mg b.i.d. wk 2	Famotidine 20 mg b.i.d. wk 4	Famotidine 20 mg b.i.d. wk 8	Famotidine 40 mg b.i.d. N	Famotidine 40 mg b.i.d. wk 2	Famotidine 40 mg b.i.d. wk 4	Famotidine 40 mg b.i.d. wk 8	Ranitidine N	Ranitidine 150 mg b.i.d. wk 2	Ranitidine 150 mg b.i.d. wk 4	Ranitidine 150 mg b.i.d. wk 8
Antwerp	Montreal	9	2 (33)	5 (71)	6 (100)	8	3 (38)	6 (100)	6 (100)	6	1 (17)	6 (100)	6 (100)	4	0 (0)	2 (33)	4 (67)
Dortmund	Hamburg	12	7 (58)	11 (92)	11 (92)	9	6 (67)	8 (89)	8 (89)	11	6 (82)	11 (100)	11 (100)	8	4 (50)	7 (88)	7 (88)
Paul	Ingolstadt	12	7 (58)	10 (83)	10 (83)	12	7 (58)	9 (75)	11 (92)	12	8 (67)	9 (75)	10 (83)	12	5 (58)	10 (83)	10 (83)
Simon	Heidelberg	13	8 (62)	9 (69)	13 (100)	13	9 (69)	11 (85)	12 (92)	13	7 (54)	11 (85)	13 (100)	13	9 (69)	12 (92)	12 (92)
Cremo	Dublin	7	4 (57)	6 (86)	7 (100)	9	3 (33)	6 (67)	8 (89)	8	5 (63)	6 (75)	7 (88)	9	2 (22)	6 (66)	7 (78)
Brenner Pony	Milan	9	2 (22)	8 (89)	9 (100)	9	2 (22)	8 (67)	9 (100)	9	4 (44)	9 (100)	9 (100)	9	5 (56)	9 (100)	9 (100)
SUBTOTAL	--	59	30 (51)	50 (85)	56 (95)	56	30 (52)	46 (79)	54 (93)	59	30 (50)	52 (88)	56 (95)	55	25 (45)	45 (77)	49 (89)
*Pool	-	181	52 (29)	114 (63)	154 (85)	189	64 (34)	125 (77)	170 (90)	188	75 (40)	149 (79)	171 (91)	190	70 (37)	143 (75)	173 (91)
TOTAL	--	240	82 (34)	164 (68)	210 (88)	247	94 (38)	191 (77)	229 (92)	247	109 (44)	201 (81)	227 (92)	245	95 (39)	188 (76)	222 (90)

*All other Investigators Combined.

(c) Relief of pain: the percentage of patients relieved of day pain (figure 39) and night pain (figure 40) was the same at all recorded intervals for all 4 treatments. Contrary to what one might expect, time to relief of day pain (table 39) was no shorter in patients whose pain was mild on entry than in those with moderate to severe pain on entry, except for patients receiving ranitidine in whom the more severe the pain, the longer the time to relief. Time to relief of night pain was, however, more rapid with all treatments in patients with initially mild pain than in those with moderate or severe pain.

Figure 39

PERCENTAGE OF PATIENTS WITH NO DAY PAIN

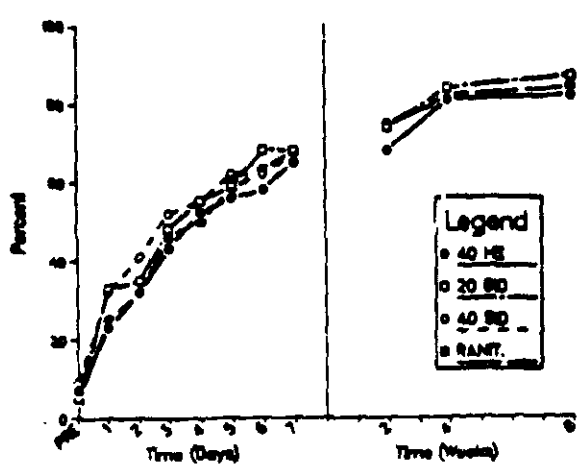


Figure 40

PERCENTAGE OF PATIENTS WITH NO NIGHT PAIN

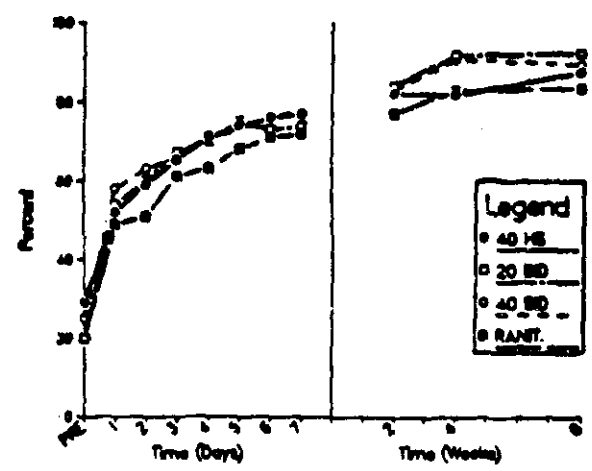


TABLE 39

Incidence of, and Median, Time to Relief of Pain (Days)

		FAMOTIDINE 40 HS (n = 240)	FAMOTIDINE 20 BID (n = 247)	FAMOTIDINE 40 BID (n = 247)	RANITIDINE 150 BID (n = 246)
Day Pain					
Incidence (%)		224 (93)	235 (95)	224 (91)	234 (95)
Baseline -	None[a]	1.0 (n = 16)	1.0 (n = 12)	1.0 (n = 23)	2.5 (n = 12)
	Mild	11.0 (n = 56)	6.0 (n = 48)	5.0 (n = 51)	4.5 (n = 62)
	Moderate	7.0 (n = 119)	6.0 (n = 112)	7.0 (n = 108)	7.0 (n = 100)
	Severe	7.0 (n = 51)	7.0 (n = 75)	7.0 (n = 65)	10.0 (n = 72)
	Total	7.0 (n = 240)	6.0 (n = 247)	6.0 (n = 247)#	7.0 (n = 246)
Night Pain					
Incidence (%)		171 (71)	197 (80)	188 (75)	197 (80)
Baseline -	None	1.0 (n = 69)	1.0 (n = 50)	1.0 (n = 62)	1.0 (n = 49)
	Mild	3.0 (n = 37)	3.0 (n = 50)	3.0 (n = 51)	3.0 (n = 52)
	Moderate	5.0 (n = 80)	5.5 (n = 86)	6.0 (n = 69)	14.0 (n = 85)
	Severe	7.0 (n = 54)	4.0 (n = 60)	7.0 (n = 65)	6.0 (n = 80)
	Total	3.5 (n = 240)	3.0 (n = 247)**	3.0 (n = 247)**	5.0 (n = 246)

[a] Some patients had no pain at baseline but had pain at one or more subsequent timepoints.

** Significantly shorter than the ranitidine group ($p < .01$).

Significantly shorter than the famotidine 40 HS group ($p < .05$)

(d) Antacid consumption: the percentage of patients receiving antacid therapy was consistently greater with ranitidine than with famotidine during the first 4 weeks, after which very few patients were still taking antacids (figure 41). During the first 2 weeks the mean number of days in which antacid therapy was taken was significantly greater with the patients receiving ranitidine than with those receiving the 2 b.i.d. doses of famotidine but the differences amount to only a fraction of a day (table 40). No difference emerged between ranitidine and the 40 h.s. dose of famotidine.

(c) Relief of pain: the percentage of patients relieved of day pain (figure 39) and night pain (figure 40) was the same at all recorded intervals for all 4 treatments. Contrary to what one might expect, time to relief of day pain (table 39) was no shorter in patients whose pain was mild on entry than in those with moderate to severe pain on entry, except for patients receiving ranitidine in whom the more severe the pain, the longer the time to relief. Time to relief of night pain was, however, more rapid with all treatments in patients with initially mild pain than in those with moderate or severe pain.

Figure 39

PERCENTAGE OF PATIENTS WITH NO DAY PAIN

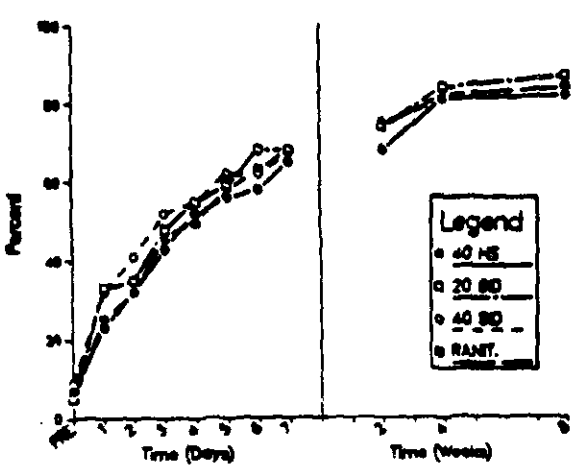


Figure 40

PERCENTAGE OF PATIENTS WITH NO NIGHT PAIN

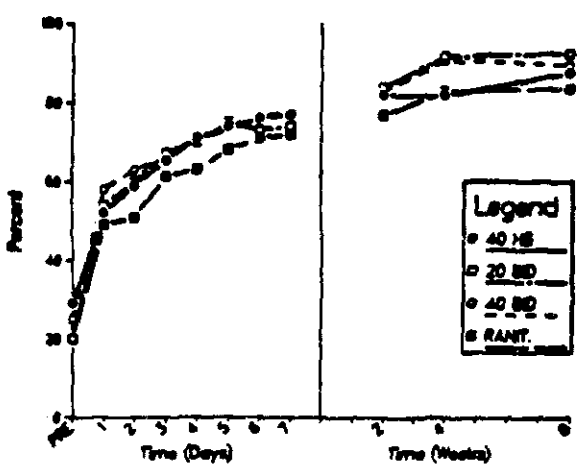


TABLE 39

Incidence of, and Median, Time to Relief of Pain (Days)

		FAMOTIDINE 40 HS (n = 248)	FAMOTIDINE 20 BID (n = 247)	FAMOTIDINE 40 BID (n = 247)	RANITIDINE 150 BID (n = 246)
Day Pain					
Incidence (%)		224 (90)	235 (95)	226 (91)	234 (95)
Baseline *	None	1.0 (n = 16)	1.0 (n = 12)	1.0 (n = 23)	2.5 (n = 12)
	Mild	11.0 (n = 56)	6.0 (n = 48)	5.0 (n = 51)	4.5 (n = 62)
	Moderate	7.0 (n = 119)	6.0 (n = 112)	7.0 (n = 108)	7.0 (n = 100)
	Severe	7.0 (n = 51)	7.0 (n = 75)	7.0 (n = 65)	10.0 (n = 72)
	Total	7.0 (n = 248)	6.0 (n = 247)	6.0 (n = 247)#	7.0 (n = 246)
Night Pain					
Incidence (%)		171 (71)	197 (80)	185 (75)	197 (80)
Baseline *	None	1.0 (n = 69)	1.0 (n = 50)	1.0 (n = 62)	1.0 (n = 49)
	Mild	3.0 (n = 37)	3.0 (n = 50)	3.0 (n = 51)	3.0 (n = 52)
	Moderate	5.0 (n = 88)	5.5 (n = 86)	6.0 (n = 69)	14.0 (n = 65)
	Severe	7.0 (n = 54)	6.0 (n = 60)	7.0 (n = 65)	6.0 (n = 80)
	Total	3.5 (n = 248)	3.0 (n = 247)**	3.0 (n = 247)**	5.0 (n = 246)

* Some patients had no pain at baseline but had pain at one or more subsequent timepoints.
** Significantly shorter than the ranitidine group ($p < .01$).
\# Significantly shorter than the famotidine 40 HS group ($p < .05$)

(d) Antacid consumption: the percentage of patients receiving antacid therapy was consistently greater with ranitidine than with famotidine during the first 4 weeks, after which very few patients were still taking antacids (figure 41). During the first 2 weeks the mean number of days in which antacid therapy was taken was significantly greater with the patients receiving ranitidine than with those receiving the 2 b.i.d. doses of famotidine but the differences amount to only a fraction of a day (table 40). No difference emerged between ranitidine and the 40 h.s. dose of famotidine.

Figure 41
Percentage of Patients Receiving Antacid Therapy

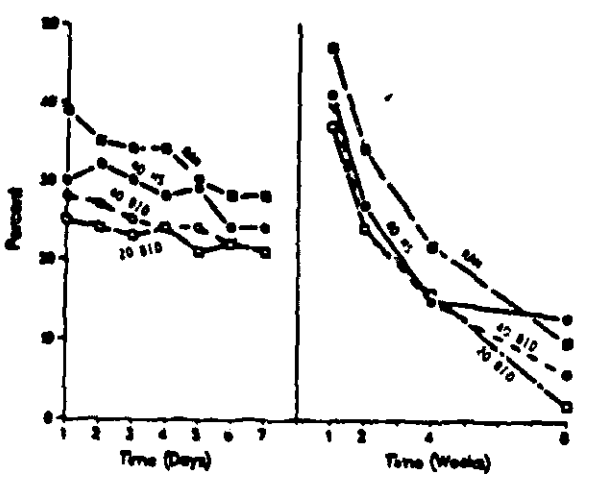


TABLE 40

Mean Days of Antacid Therapy, Mean ± Standard Deviation

WEEK	FAMOTIDINE 40 HS N	FAMOTIDINE 40 HS MEAN	FAMOTIDINE 20 BID N	FAMOTIDINE 20 BID MEAN	FAMOTIDINE 40 BID N	FAMOTIDINE 40 BID MEAN	RANITIDINE 150 BID N	RANITIDINE 150 BID MEAN	NUMBER OF DAYS DIFFERENCE BETWEEN 40 BID & RANITID
1	241	2.0 ± 2.7	250	1.6 ± 2.5**	249	1.7 ± 2.6*	247	2.3 ± 3.0	- 0.3
2	227	1.3 ± 2.4	239	0.9 ± 2.1**	237	1.1 ± 2.3*	237	1.6 ± 2.7	- 0.3
4	132	0.8 ± 2.0	140	1.0 ± 2.3	113	0.7 ± 1.9	129	1.2 ± 2.5	- 0.4
8	53	0.7 ± 1.9	41	0.20 ± 1.1	28	0.5 ± 1.8	40	0.7 ± 2.1	- 0.0

*,** Significantly different from the ranitidine group (p .05, p .01, respectively).
Significantly different from the 40 HS group (p .05).
Mean number of days of antacid therapy is the 7-day period ending the relative day of the pain measurements taken at this week. Since some patients have no pain measurements, numbers may differ.
N Number of patients evaluated.

e. Summary: 1,031 patients were entered into a multicenter trial of 3 doses of famotidine (40 mg h.s., 20 mg b.i.d. and 40 mg b.i.d.) vs ranitidine 150 mg b.i.d. in the short-term treatment of duodenal ulcer. The incidence of healing was:

WK	Fam 40 HS	Fam 20 BID	Fam 40 BID	Ran 50 BID
4	68%	77%	81%	76%
8	87%	92%	92%	90%

Thus the incidence of healing with ranitidine at the important 4 week follow-up was of the same order as that with famotidine 20 mg b.i.d. and 40 mg b.i.d. but was higher than with the sponsor's recommended dose of 40 mg h.s. The percentage of patients relieved of both day and night pain was in the neighborhood of 60% at the end of the first week and 80% at the end of 8 weeks with all 4 treatments. The time to relief of day pain in famotidine-treated patients was generally not shorter when the pain was initially mild than when it was moderate or severe, averaging 6-7 days. In patients receiving ranitidine the average time to relief of severe pain was 18 days contrasted with 4.5 days for mild pain. The average number of days in which patients took antacids differed by a fraction of a day among the 4 treatment groups, a clinically meaningless difference. The percentage of patients receiving antacids during the first 2 weeks of treatment was significantly less in patients receiving famotidine 20 mg b.i.d. than in those receiving ranitidine, but at no time point was there an advantage of the sponsor's recommended dose (40 mg h.s.) over ranitidine in the number of patients requiring concomitant antacid therapy. The incidence of drug-related adverse events requiring withdrawal of patients from famotidine treatment was less than 1%.

An interesting difference between the conduct of the U.S. and foreign trials in the short-term treatment of duodenal ulcer is that twice as many U.S. investigators contributed 10 or fewer patients, while twice as many foreign investigators contributed 11 or more patients. It would be instructive to know whether this difference is because the foreign investigators had more time to complete the assigned number of patients, had more patients available to them, are more persuasive in convincing patients to enter clinical trials, or whether patients are more easily persuaded to participate when the control substance is a drug of known effectiveness rather than a placebo.

2. Protocol No. 503-00

a. Title of study: A double-blind study in out-patients to compare famotidine with placebo in the long-term maintenance treatment of duodenal ulcer (weeks 1-24).

b. Design of study: the procedure was identical with that of the U.S. multi-center trial of prevention of recurrence except that only 1 dose of famotidine, 20 mg h.s., was compared with placebo.

c. Investigators: 64 of the 68 investigators listed in the short-term trial participated.

d. Results

(1) Comparability of patient groups (table 41): there were 306 patients on famotidine, 339 on placebo. The groups were comparable in all relevant respects.

TABLE 41

Comparability of Treatment Groups

	FAMOTIDINE 20 MG (N=306[a])	PLACEBO (N=339[a])
Age (Years), Mean	42.5	43.9
Sex		
Males	222 (73%)	217 (64%)
Females	84 (27%)	102 (30%)
Treatment in the Acute Study		
Famotidine 40 MG	76 (25%)	77 (23%)
Famotidine 20 BID	67 (22%)	100 (30%)
Famotidine 40 BID	82 (26%)	85 (25%)
Ranitidine Base 150 BID	79 (26%)	75 (22%)
Week Ulcer Healed in the Acute Study		
Week 2	133 (44%)	129 (38%)
Week 4	120 (42%)	141 (42%)
Week 8 or later	43 (14%)	67 (20%)
Smoking[b]	168 (55%)	208 (62%)
Drinking[b]	126 (41%)	166 (49%)
Initial Ulcer Size[b] (cm), Mean	0.91	0.90
Number of Ulcers[b]		
One	276 (91%)	304 (90%)
Two or More	28 (9%)	33 (10%)
Age at First Ulcer[b] (Years)		
Mean	30.2	30.2
Median	25.0	28.0
Duration of Ulcer Disease[b] (Years)		
Mean	5.4	5.7
Median	3.0	3.0
Ulcer History[b]		
None	82 (27%)	98 (29%)
One Previous Episode	83 (27%)	88 (26%)
Multiple Previous Episodes	139 (46%)	151 (45%)
Race		
Caucasian	270 (88%)	311 (92%)
Black	8 (3%)	7 (2%)
Hispanic	5 (2%)	7 (2%)
Other	23 (7%)	14 (4%)
Other Pathology in the Esophagus	19 (6%)	23 (7%)
Other Pathology in the Stomach	39 (13%)	31 (9%)
Other Pathology in the Duodenum	166 (54%)	191 (57%)

[a]Maximum counts, some patients had no information for some variables.
[b]Status at the beginning of the short term study.

An interesting difference between the conduct of the U.S. and foreign trials in the short-term treatment of duodenal ulcer is that twice as many U.S. investigators contributed 10 or fewer patients, while twice as many foreign investigators contributed 11 or more patients. It would be instructive to know whether this difference is because the foreign investigators had more time to complete the assigned number of patients, had more patients available to them, are more persuasive in convincing patients to enter clinical trials, or whether patients are more easily persuaded to participate when the control substance is a drug of known effectiveness rather than a placebo.

2. Protocol No. 503-00

a. Title of study: A double-blind study in out-patients to compare famotidine with placebo in the long-term maintenance treatment of duodenal ulcer (weeks 1-24).

b. Design of study: the procedure was identical with that of the U.S. multi-center trial of prevention of recurrence except that only 1 dose of famotidine, 20 mg h.s., was compared with placebo.

c. Investigators: 64 of the 68 investigators listed in the short-term trial participated.

d. Results

(1) Comparability of patient groups (table 41): there were 306 patients on famotidine, 339 on placebo. The groups were comparable in all relevant respects.

TABLE 41

Comparability of Treatment Groups

	FAMOTIDINE 20 MG (N=306[a])	PLACEBO (N=339[a])
Age (Years), Mean	43.5	43.9
Sex		
Males	222 (73%)	237 (69%)
Females	84 (27%)	102 (30%)
Treatment in the Acute Study		
Famotidine 40 mg	76 (25%)	77 (23%)
Famotidine 20 BID	67 (22%)	100 (30%)
Famotidine 40 BID	82 (26%)	85 (25%)
Ranitidine Dose 150 BID	79 (26%)	75 (22%)
Week Ulcer Healed in the Acute Study		
Week 2	133 (44%)	129 (38%)
Week 4	128 (42%)	141 (42%)
Week 6 or later	43 (14%)	67 (20%)
Smoking[b]	168 (55%)	200 (62%)
Drinking[b]	126 (41%)	166 (49%)
Initial Ulcer Size[b] (cm), Mean	0.91	0.90
Number of Ulcers[b]		
One	276 (91%)	304 (90%)
Two or More	28 (9%)	33 (10%)
Age at First Ulcer[b] (Years)		
Mean	38.2	38.2
Median	35.0	38.0
Duration of Ulcer Disease[b] (Years)		
Mean	5.4	5.7
Median	3.0	3.0
Ulcer History[b]		
None	82 (27%)	98 (29%)
One Previous Episode	83 (27%)	88 (26%)
Multiple Previous Episodes	139 (46%)	151 (45%)
Race		
Caucasian	270 (88%)	311 (92%)
Black	8 (3%)	7 (2%)
Hispanic	5 (2%)	7 (2%)
Other	23 (7%)	14 (4%)
Other Pathology in the Esophagus	19 (6%)	23 (7%)
Other Pathology in the Stomach	30 (10%)	31 (9%)
Other Pathology in the Duodenum	168 (54%)	191 (57%)

[a]Maximum counts, some patients had no information for some variables.
[b]Status at the beginning of the short term study.

(2) Exclusions from analysis of effectiveness (table 42): 38/306 (12%) of patients receiving famotidine and 33/309 (10%) of patients receiving placebo were excluded, primarily because of various protocol violations, the most common of which were (a) failure to take the drug as prescribed and (b) taking forbidden concomitant medications. The percentage lost was in the same range as that in the U.S. trial.

TABLE 42

Exclusions from Analysis of Effectiveness

	Number of Patients (%) FAMOTIDINE N=306	PLACEBO N=339
Off Drug	16	19
Concomitant Medication	5	8
No Final Endoscopy	4	1
Patient Unreliable	4	3
Other Protocol Violations	7	5
Total	38(12)	33(10)

(3) Safety

(a) Vital signs: other than an increase in body weight, of no clinical import, in patients receiving famotidine compared with patients receiving placebo, there was no difference between the treatments with regard to change from baseline or difference from each other.

(b) Clinical adverse experiences (table 43) occurred with somewhat higher frequency in patients on famotidine (25%) than on placebo (19%); the difference is not statistically significant. Headache, the most common CNS symptom, occurred with equal frequency in the 2 groups (famotidine 2.6%, placebo 2.9%).

TABLE 43

Number of Patients with Adverse Experiences (%)

BODY SYSTEM	Famotidine 20 MG N = 306	Placebo N = 339
Central Nervous	16 (5.2)	20 (5.9)
Cardiovascular	3 (1.0)	1 (0.3)
Digestive	14 (4.6)	21 (6.2)
Respiratory	21 (6.9)	8 (2.4)
Tegumentary	7 (2.3)	6 (1.8)
Musculoskeletal	6 (2.0)	2 (0.6)
Hemic/Lymphatic	1 (0.3)	0
Special Senses	4 (1.3)	4 (1.2)
Urogenital	4 (1.3)	2 (0.6)
TOTAL	76 (25)	64 (19)

Symptoms evaluated by the investigator as possibly, probably or definitely drug-related were recorded in 5/306 (1.6%) of patients receiving famotidine, 9/339 (2.7%) of patients receiving placebo. The only really troublesome adverse clinical event in patients receiving famotidine was alopecia in one patient; however, it was also reported in one patient receiving placebo. Among patients 65 years of age or older clinical adverse experiences occurred in 8/18 (44%) on famotidine, 5/17 (29%) on placebo; however, the adverse experiences reported in this age group appeared to be related not to a drug-effect but rather to diseases associated with advancing age such as myocardial infarction, traumatic arthropathy, insomnia, Parkinson's disease and neoplasia. This is a reflection of the FDA requirement that all adverse events occurring during a clinical trial be reported; for example injury or death from a gunshot wound or a traffic accident while a patient is in a clinical trial must be reported as an adverse event which it obviously is, but which equally obviously has nothing to do with the treatment. Since such events could occur with equal frequency in patients receiving a drug as in those receiving a placebo, it is not surprising that, in a clinical trial of a drug as safe as famotidine, the percent of patients withdrawn because of adverse experiences in this trial was the same with famotidine, 9/306 as with placebo, 8/339 (2.4%). Interpretation of these numbers is complicated by the fact that investigators differ in their assessments of possibly/probably drug-related effects. These differences are illustrated in the 8 patients in whom serious adverse events were reported:

A 50 year old man receiving famotidine experienced 2 episodes of hematemesis and hematochezia on day 34. Endoscopy 2 days later revealed a 2.0 cm duodenal ulcer with signs of bleeding. Following gastric resection the patient had an uneventful recovery. The investigator assessed this occurrence as probably not drug-related.

The duodenal ulcer in a 50 year old man with tarry stools on entry into the short-term trial healed complete on ranitidine; the patient was enrolled in the maintenance study on famotidine. On day 85 endoscopy revealed hemorrhagic gastritis. On day 123 the patient reported fulness; endoscopy showed bleeding varices in the gastric fundus. Carcinoma of the pancreas was suspected and was confirmed at surgery on the following day. The investigator's opinion was that this was probably not a drug-related event.

A 70 year old man was hospitalized because of chest pain on day 8 of treatment with famotidine. There were no significant changes in the ECG; enzyme levels were not raised. After discharge, medication was restarted. On day 77 the patient again experienced chest pain and was withdrawn from the study. He later underwent surgery for pneumothorax. The investigator thought that this occurrence was probably not drug related.

A 48 year old man experienced asthenia, headache and dizziness during treatment with ranitidine in the short-term study. In the maintenance study he was randomized to receive famotidine. On day 36 he was withdrawn from the study because of severe asthenia and an ALAT of 592. A diagnosis of hepatitis B was established. Eight months later the ALAT was still elevated (450) but no clinical symptoms were present. The investigator concluded that the hepatitis was definitely not drug-related.

A 71 year old man taking several drugs for peripheral vascular disease was randomized to the famotidine treatment group. On day 70 he suffered a myocardial infarction and died within 2 hours. The investigator concluded that this was definitely not drug-related.

A 69 year old man with a history of perforated duodenal ulcer complicated by a right subphrenic abscess was entered into the maintenance trial despite the fact that after 4 weeks of treatment with famotidine 40 mg h.s. in the short-term trial his abdominal pain had not improved and endoscopic examination was not possible because of pyloric deformity. On day 10 the patient was hospitalized for hematemesis and was found to have bronchial carcinoma metastasic to the liver. The investigator concluded that this occurrence was definitely not drug-related.

A 59 year old woman experienced a myocardial infarction on day 24 of treatment with placebo. She subsequently recovered. The investigator assessed this experience as probably not drug-related.

A 56 year old man receiving placebo was found on day 25 to have cancer of colon. The investigator believed that this was definitely not drug-related.

It is obvious from the above summaries that these serious clinical adverse experiences were not drug-related, even though the assessment "probably not" is tantamount to "possibly yes."

(c) Laboratory adverse experiences (table 44): the only noteworthy observation was the occurrence of abnormal results of tests of hepatic injury in 15/255 (6%) of patients receiving famotidine vs 0/271 with placebo. If these numbers are correct, famotidine will bear watching for possible hepatotoxicity; however, none of the changes were serious and only one patient was withdrawn from the study because of a suspect laboratory value. Among the 18 patients 65 years or older receiving famotidine there were no laboratory adverse events.

TABLE 44

Laboratory Adverse Events/ ...ers at Risk

	Famotidine 20 MG N = 306	Placebo N = 330
Hematologic	11/256	10/260
Renal Function	1/151	3/156
Hepatic	15/255	0/271
Metabolic	1/110	2/116
Urogenital	2/258	1/269

(4) Effectiveness

(a) Prevention of recurrence: famotidine significantly decreased the rate and the incidence of recurrence of duodenal ulcer (table 45) compared to placebo. In patients receiving placebo the incidence of recurrence within the first 4 months was an astonishing 60% vs 20% of those receiving famotidine. Data extending to almost 9 months put the incidence of recurrence with placebo (74%) at more than twice that with famotidine; while this is a highly significant difference favoring famotidine, it is far from an impressive achievement, especially since in patients treated with famotidine there was a substantial increase in recurrences from the end of 6 months onward.

TABLE 45

Number of Patients Who Relapsed (%)*
(Life Table Rate)

Months (Day Range) on Treatment	FAMOTIDINE 20 MG (N = 306)	PLACEBO (N = 329)
Month 1 (Days 1-28)	1 (0.3)	21 (6)
Month 2 (Days 29-56)	7 (2)	60 (19)
Month 3 (Days 57-84)	24 (9)	103 (33)
Month 4 (Days 85-112)	50 (19)	185 (62)
Month 5 (Days 113-140)	55 (21)	193 (65)
Month 6 (Days 141-168)	58 (22)	198 (67)
After Month 6 (Days 169-245)	82 (34)	215 (74)

*All Patients Treated Analysis

(b) Relief of pain (table 46): as would be expected from the data on recurrence of ulcers, famotidine was much more effective than placebo in preventing recurrence of ulcer pain. Since patients eligible for admission to the trial were those in whom the ulcer had healed during short-term treatment, the incidence of moderate to severe pain at baseline was negligible. However, the proportion of patients experiencing moderate to severe pain by the end of the study was clearly much greater in patients on placebo than in those on famotidine.

TABLE 46

Distribution of Day and Night Pain

Severity of Pain Baseline	Severity of Pain End of Study	Day Pain Famotidine	Day Pain Placebo	Night Pain Famotidine	Night Pain Placebo
None	None	161	94	192	148
None	Mild	37	56	22	46
None	Mod./Severe	23	115	13	56
Mild	None	35	15	21	10
Mild	Mild	11	7	3	5
Mild	Mod./Severe	0	12	3	3
Mod./Severe	None	2	0	4	2
Mod./Severe	Mild	1	1	0	0
Mod./Severe	Severe	0	1	0	1

Significant difference between treatments, p<.01, in favor of famotidine for both day pain and night pain.

(c) Antacid consumption: the proportion of patients who took antacids at any time during the trial was significantly higher in patients on placebo (49%) than in those on famotidine (33%), p 0.01. However, the number of doses taken is not reported.

e. Summary: in a multicenter double-blind placebo controlled trial of famotidine 20 mg h.s. (306 patients) vs placebo (339 patients), famotidine was statistically significantly more effective than placebo over a period of 6-9 months in preventing recurrence of duodenal ulcer, relapse of symptoms and requirement for concomitant antacid therapy. Nevertheless, the incidence of recurrence with famotidine, 22% at the end of 6 months, 34% at the end of an additional 3 months, suggests that by the end of a year the incidence of recurrence may well be higher than the 25-35% incidence reported in clinical trials of other drugs.

3. Study No. 5007

a. Title of study: Comparison of famotidine vs placebo in the short-term treatment of gastric ulcer.

b. Design of study: patients with clinical symptoms and endoscopic evidence of a gastric ulcer measuring 0.5-2.5 cm were allocated randomly to receive either famotidine 40 mg or matching placebo at bedtime. Each patient received a bottle of antacid tablets to be taken only if additional symptomatic relief was required. The maximum number of tablets allowed per day had a neutralizing capacity of 88 mEq/day.

Exclusions and procedures at the initial (screening) visit were the same as in the protocol for short-term treatment of duodenal ulcer. Assessment of clinical symptoms and endoscopy were performed at weeks 4, 6 and 8 unless complete healing of the ulcer was demonstrated at the previous visit. At each visit patients were given take-home cards to record day and night pain, number of antacid tablets taken and any adverse experiences. Adverse symptoms and laboratory events were evaluated by the investigator.

An ulcer was considered healed if there was complete epithelization of the crater, regardless of the emergence or persistence of gastritis or erosions. A biopsy was performed at the initial visit, and, at the discretion of the investigator, at subsequent visits, to rule out gastric carcinoma.

Day and night pain and overall therapeutic responses were scored using the same grading system described above in the foreign short-term trial of healing of duodenal ulcer.

Investigators (table 47): the 44 investigators from 14 countries are all qualified by training and experience to conduct a clinical trial of this type.

Table 47

Country/Name	Affiliation	Location
Argentina		
M. Delgado, A.O.F.	Director of the Hospital	Ramos Mejia Hospital, Buenos Aires
Kohan, S.	Chief of Gastroenterology Dept.	Piravano Hospital, Buenos Aires
Segal, J.E.	Chief of Gastroenterology Dept.	Durand Hospital, Buenos Aires
Austria		
Meinschel, E.	Internist	Hanusch Hospital, Vienna
Reicher, W.	Director of Endoscopical Ambulance	Wilhelminen Hospital, Vienna
Schultze, K.	Specialist in Internal Medicine	Hanusch Hospital, Vienna
Brazil		
Castro, L.	Gastroenterologist	Federal University of Minas
Vilela, N.P.	Gastroenterologist	Hospital Sao Paulo
Canada		
Archambault, A.	Head of Gastroenterology	Maisonneuve-Rosemont, Hospital Montreal
Marcon, N.M.	Head of Gastroenterology	The Wellesley Hospital, Toronto
Colombia		
Aponte, L.	Endoscopist/Gastroenterologist	Carrera 18 No. 80-47, Bogota
Denmark		
Hoilund, N.	Head Surgeon	Arhus Council Hospital, Arhus
Holland		
Kettner, M.	Internist	Gasthuis Middelburg, Middelburg
Van Bentum	Gastroenterologist	De Stadsmaten Hospital, Enshede
Wesdorp, I.C.E.	Gastroenterologist	Andreas Hospital, Amsterdam
Italy		
Bagiloni, A.	Surgeon, Lecturer	Hospital Generale, Provinciale, "SS Trinita", Sora
Barbara, L.	Director of Gastroenterology	Hospital Sant'Orsola, Bologna
Bianchi-Porro, G.	Director of Gastroenterology	Hospital L. Sacco, Milan
Blasi, A.	Director of Gastroenterology	Hospital Vittorio, Emanuele II, Catania
Carotenuto, F.	Head Surgeon	Municipal Hospital of Cassino
Chelli, R.	Chief of Gastroenterology	Hospital S. Martino, Genova
Dal Monte, P.R.	Head Gastroenterologist	Hospital Bellaria, Bologna
Francavilla, A.	Head of Gastroenterology	Cattedra de Malattie, Gari Apparato
Matarazzo, P.F.	Assistant Surgeon	Municipal Hospital of Formia
Mazzacca, G.	Division of Gastroenterology	School of Medicine, Naples
Paoluzi, P.	Gastroenterologist/Endoscopist	II Clinical Medica Universita
Speranza, V.	Head of Surgical Clinic	VI Clinical Chirurgica University
Vagni, V.	Consultant Endoscopist, Lecturer	Municipal Hospital Castellana
Verme, G.	Professor, Head Physician	Hospital Molinette, Torino
Finland		
Pikkarainen, P.	Head of Gastroenterology	University Central Hospital, Kuopio
Krekela, I.	Physician	University Central Hospital, Oulo
France		
Paris, J.C.	Head of Gastroenterology	Centre Hospitalier Regional, Lille
Sarles, H.	Professor, Dept. Head	Hospital of Sante Marseille Marguerite
Germany		
Dammann, H.G.	Head of Gastroenterology	Bethanien Hospital, Hamburg
Jakob, G.	Head of Gastroenterology	District Hospital, Eichstaett
Niederer, S.E.	Professor of Gastroenterology	Medical University Poliklinik, Bonn
Ottenjann, R.	Head of Dept. of Internal Medicine	Municiple Hospital Mue
Paul, F.	Professor, Head of Medical Clinic II	Klinik Ingolstadt, Ingolstadt/Donau
Schwetz, E.	Internist/Gastroenterologist	Gastroenterology-Proktology, Regensburg
Stemm, B.	Specialist for Gastroenterology	Medical University, Klinik, Heidelburg
Stadelmann, O.	Head of Gastroenterology	ChA d. Medical Klinik Fuerth
Mexico		
Villalobos, J.	Head of Gastroenterology	National Institute of Nutrition, Mexico, D.F.
South Africa		
Hinder, R.A.	Gastroenterologist	Johannesburg Hospital, Parktown
Mal, C.J.C.	Professor, Gastroenterologist	University Hospital, Bloemfontein
Sweden		
Hradsky, M.	Chief of Gastroenterology Unit	Falu Hospital, Falun

d. Results

(1) Comparability of the treatment groups (table 48): case report forms for 336 patients were available by the cut-off date December 21, 1984, 167 randomized to famotidine, 169 to placebo. The 2 groups were comparable in most respects except that there was a significantly higher proportion of drinkers among patients in the pl

TABLE 48

Comparability of Treatment Groups

	Famotidine N = 167	Placebo N = 169
Age (yrs)		
Mean	52.2	51.5
Median	56.0	54.0
Sex		
Males	104	104
Females	63	65
Weight (kg)	66.3	66.2
Smoking	98 (59%)	104 (62%)
Alcohol	70* (42%)	100 (57%)
Initial Ulcer Size (cm)[a]		
Mean	1.15	1.06
Median	1.00	1.00
Number of Ulcers		
One	148 (89%)	159 (94%)
Two or more	19 (11%)	10 (6%)
Age at First Ulcer (yrs)		
Mean	48.2	47.2
Median	52.0	47.0
Duration of Ulcer Dis.(yrs)		
Mean	4.0	4.4
Median	0.0	0.0
Ulcer History		
None	85 (51%)	86 (51%)
Single	41 (25%)	37 (22%)
Multiple	41 (25%)	46 (27%)
Ulcer pathology, Esophagus	13 (8%)	11 (7%)
Ulcer pathology, Stomach	61 (37%)	61 (36%)
Ulcer pathology, Duodenum	31 (19%)	29 (17%)

[a] For patients with more than one ulcer, this was the size of the largest ulcer.

* Significantly different from the placebo group (p < 0.01).

(2) Exclusions from analysis of effectiveness (table 49): 11% of the patients randomized to receive famotidine and 14% of those randomized to placebo were excluded for various protocol violations. These percentages are not excessive compared with numbers reported in other NDAs for studies of this type.

TABLE 49

Exclusions from analysis of effectiveness

Reasons	Famotidine N=167	Placebo N=169
Off drug	2	4
Ulcer 2.5 cm	5	3
Ulcer 0.5 cm	3	3
Cancer at entry	1	5
Concomitant medication	3	3
Endoscopy out of range	2	1
Other	2	5
Total (%)	18 (11)	24 (14)

(3) Safety

(a) Vital signs (table 50): the only change in vital signs after treatment was a clinically inconsequential mean weight gain of 0.4 kg in patients on famotidine.

TABLE 50

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE
Pulse rate	Famotidine	161	74.7	74.9	0.2
	Placebo	160	74.7	75.1	0.4
Systolic BP	Famotidine	161	133.0	131.8	-1.2
	Placebo	161	131.8	132.2	0.4
Diastolic BP (mmHg)	Famotidine	159	80.6	80.6	-0.2
	Placebo	159	80.3	81.5	1.2
Weight (kgs)	Famotidine	161	66.3	66.7	0.4MM,*
	Placebo	162	66.2	66.1	-0.1

* Significant difference between treatment groups ($p < 0.05$).
MM Significant increase from baseline ($p < 0.01$).

(b) Adverse signs/symptoms were no more frequent among patients receiving famotidine than among those receiving placebo, totaling 13% of the patients entered in either group (table 51). The proportions considered by the investigators to be possibly/probably drug-related were also the same for each group (famotidine 7%, placebo 6%). The investigators considered withdrawals drug-related in 1 famotidine-treated patient (0.6%) and 5 placebo patients (3%) (table 52). Among the adverse reactions considered serious, 3 occurred in patients receiving famotidine, the first of which was a 55 year old man withdrawn from the study after 29 days of treatment after surgical removal of a melanoma of the skin, the second a 26 year old women withdrawn at the first follow-up visit because endoscopic biopsy revealed multiple granulomatous ulcers compatible with a diagnosis of Crohn's gastritis, the 3rd a 42 year old paraplegic male who had a pulmonary embolism 12 days after entering the trial. The one patient with a serious adverse clinical reaction in the placebo group was a 39 year old man in whom, because the ulcer had not healed at 8 weeks, a biopsy was performed and found to contain carcinoma. Obviously none of these reactions could by any stretch of the imagination be considered drug-related.

TABLE 51

Clinical Adverse Experiences By Body System (%)

	FAMOTIDINE (N = 167)	PLACEBO (N = 169)
Body as a whole	1 (0.6)	3 (1.8)
Cardiovascular	1 (0.6)	1 (0.6)
Central Nervous	1 (0.6)	1 (0.6)
Digestive	9 (5.4)	7 (4.1)
Integumentary	2 (1.2)	3 (1.8)
Metabolic/Nutritional /Immune	2 (1.2)	0 (0.0)
Musculoskeletal	1 (0.6)	2 (1.2)
Nervous and Psychiatric	5 (3.0)	9 (5.3)
Respiratory	5 (2.4)	4 (2.4)
Tegumentary	2 (1.2)	2 (1.2)
Special Senses	1 (0.6)	0 (0.0)
Urogenital	3 (1.8)	2 (1.2)
Total	22 (13.2)	22 (13.0)

TABLE 52

Patients Withdrawn Due to Adverse Experience

TREATMENT GROUP	AN	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP	TOTAL POSSIBLY/PROBAB DEFINITELY
Famotidine 40 HS	39	Disorientation	Severe	Possibly	
		Muscular cramps	Severe	Probably	
		Sexual impotence	Severe	Probably	
	152	Acid regurgitation	Moderate	Definitely Not	
		Fullness	Moderate	Definitely Not	
	205	Skin melanoma	--	Definitely Not	
	293	Gastric granuloma	Severe	Definitely Not	
	310	Development of duodenal ulcer	Mild	Definitely Not	
	316	Pulmonary embolism	Severe	Definitely Not	
		Pneumonia	Severe	Definitely Not	1 (0.6)%
Placebo	63	Asthenia	Mild	Possibly	
	123	Abdominal discomfort	Severe	Definitely	
		Flatulence	Moderate	Definitely	
		Fullness	Severe	Definitely	
		Nausea	Severe	Definitely	
		Vomiting	Severe	Definitely	
	136	Headache	Severe	Probably	
		Nausea	Moderate	Possibly	
		Development of duodenal ulcers	--	Definitely Not	
	197	Nausea	Mild	Probably Not[a]	
		Duodenal ulcer	Moderate	Probably	
		Flatulence	Mild	Probably Not[a]	
		Cold	Mild	Definitely Not	
		Cough	Mild	Definitely Not	
		Fever	Moderate	Definitely Not	
	333	Vomiting	Moderate	Probably Not[a]	5 (3%)

[a]"Probably not" = "Probably"

(c) Laboratory adverse events: there were 5 abnormal laboratory reports in patients receiving famotidine, 6 in patients receiving placebo; none of these were serious or drug-related or necessitated withdrawal of the patients from the trial.

(4) Effectiveness

(a) Incidence of healing (table 53): the cumulative incidence of healing with famotidine was 45% at week 4, 62% at week 6, 77% at week 8, all statistically significantly superior to the incidence of healing in patients receiving placebo (30%, 44% and 51%) at the respective weeks.

TABLE 53

Cumulative Number Healed/Number Entered (%)

Week	Endoscopic Range, Days	Famotidine (N=167)	Placebo (N=169)	p
4	00 to 34	75 (45)	50 (30)	<0.01
6	35 to 49	104 (62)	74 (44)	<0.01
8	50 to 64	128 (77)	86 (51)	<0.01
Later	After 64	131 (78)	88 (52)	<0.01

(b) Relief of pain: the proportion of patients relieved of day pain (figure 42) was clearly higher in those receiving famotidine at all intervals from the first day of treatment through the end of the 8th week. By the end of the first week day pain was relieved in some 40% of patients on famotidine vs 20% in patients on placebo; by the end of the study the difference in the proportion of patients without day pain had narrowed between the 2 treatments to 80% vs some 65% respectively. With regard to night pain very little difference was evident between the 2 groups (figure 43). In contrast to famotidine the median number of days to relief of [illegible] was proportional to the severity

Figure 42
Percentage of Patients With No Day Pain

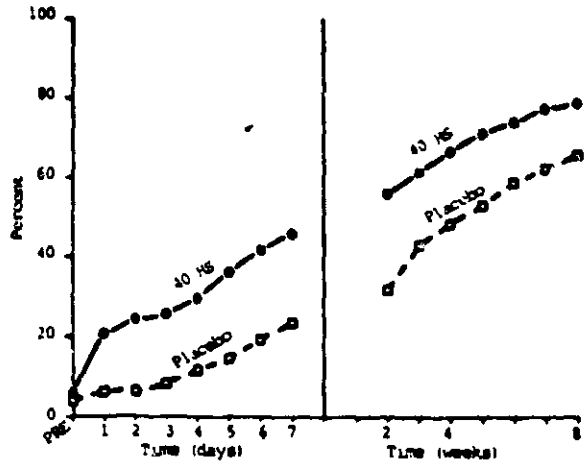
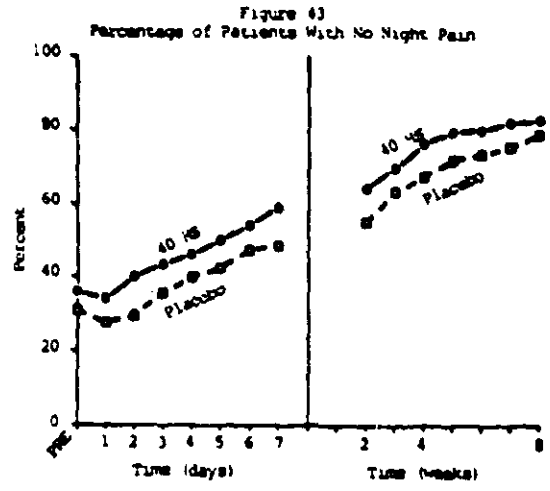


Figure 43
Percentage of Patients With No Night Pain



of pain at the outset; this was not the case in patients receiving placebo (table 54). In patients receiving famotidine, the median number of days to relief of both day and night pain was 5 in patients starting with mild pain, 14 in patients starting with moderate pain and 28 in patients starting with severe pain.

TABLE 54
Time to Relief of Pain

		FAMOTIDINE (N=149)	PLACEBO (N=145)
Baseline -	Day Pain		
	None*	1.0 (n = 9)	21.5 (n = 6)
	Mild	5.0 (n = 31)	31.5 (n = 32)
	Moderate	14.0 (n = 68)	35.0 (n = 60)
	Severe	28.0 (n = 41)	35.9 (n = 47)
	All**	14.0 (n = 149)	35.0 (n = 145)
Baseline -	Night Pain		
	None	1.0 (n = 54)	1.0 (n = 45)
	Mild	5.5 (n = 22)	18.0 (n = 30)
	Moderate	14.0 (n = 47)	21.0 (n = 41)
	Severe	28.0 (n = 26)	28.0 (n = 29)
	All**	5.0 (n = 149)	14.0 (n = 145)

* Some patients had no pain at baseline but had pain at one or more subsequent timepoints.
** Significant difference between treatment groups ($p < 0.01$)

(c) Antacid consumption: the percentage of patients taking antacids (figure 44) was quite high in both groups, but at all intervals was higher in p[illegible]on placebo than in those on famotidine. Since there are no dat[illegible]ber of antacid doses taken, it is not known whether there is [illegible]ignificance in these differences. The average number of d[illegible]umption (table 55) was statistically but not [illegible]y higher with placebo.

TABLE 55
Antacid Consumption
Mean Days of Antacid Therapy, Mean ± Standard Deviation

WEEK	Famotidine 40 HS N	MEAN	Placebo N	MEAN	Number of Days Difference Between 40 HS and Placebo
	149	2.4 ± 3.0*	145	3.2 ± 3.2	-0.8
	142	1.7 ± 2.8*	137	2.7 ± 3.2	-1.0
	5	1.4 ± 2.6*	129	2.1 ± 3.0	-0.7
	36	1.4 ± 2.7*	48	2.2 ± 3.2	-0.8

*[illegible]cantly different from the placebo group ($p < 0.05$).

Figure 42
Percentage of Patients With No Day Pain

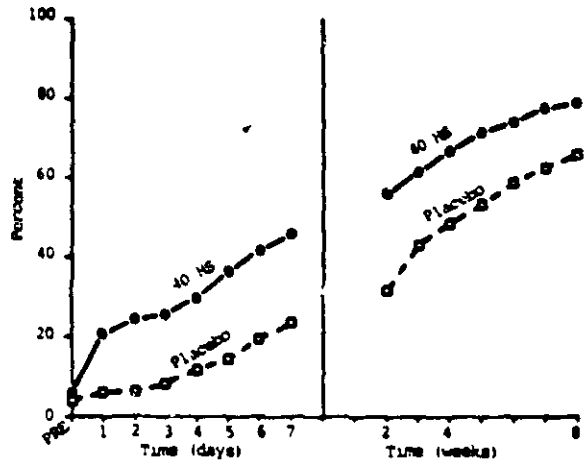


Figure 43
Percentage of Patients With No Night Pain

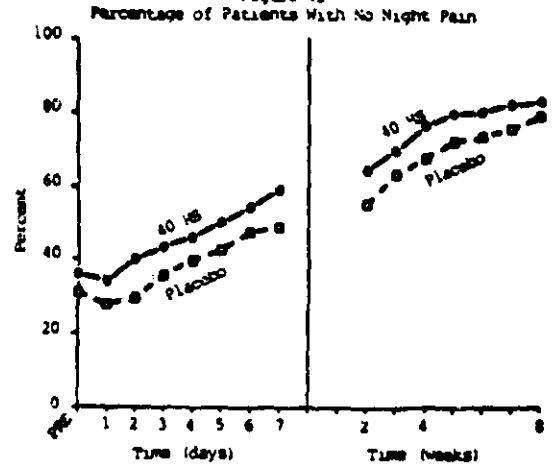


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TABLE 54
Time to Relief of Pain

		FAMOTIDINE (N=149)	PLACEBO (N=145)
Baseline -	Day Pain		
	None[a]	1.0 (n = 9)	21.5 (n = 6)
	Mild	5.0 (n = 31)	31.5 (n = 32)
	Moderate	14.0 (n = 68)	35.0 (n = 60)
	Severe	28.0 (n = 41)	35.0 (n = 47)
	All**	14.0 (n = 149)	35.0 (n = 145)
Baseline -	Night Pain		
	None	1.0 (n = 54)	1.0 (n = 45)
	Mild	5.5 (n = 22)	18.0 (n = 30)
	Moderate	14.0 (n = 47)	21.0 (n = 41)
	Severe	28.0 (n = 26)	28.0 (n = 29)
	All**	5.0 (n = 149)	14.0 (n = 145)

[a] Some patients had no pain at baseline but had pain at one or more subsequent timepoints.

** Significant difference between treatment groups ($p < 0.01$)

(c) Antacid consumption: the percentage of patients taking antacids (figure 44) was quite high in both groups, but at all intervals was higher in patients on placebo than in those on famotidine. Since there are no data on the number of antacid doses taken, it is not known whether there is any clinical significance in these differences. The average number of days of antacid consumption (table 55) was statistically but not clinically significantly higher with placebo.

Figure 44
Percent of Patients Receiving Antacid Therapy

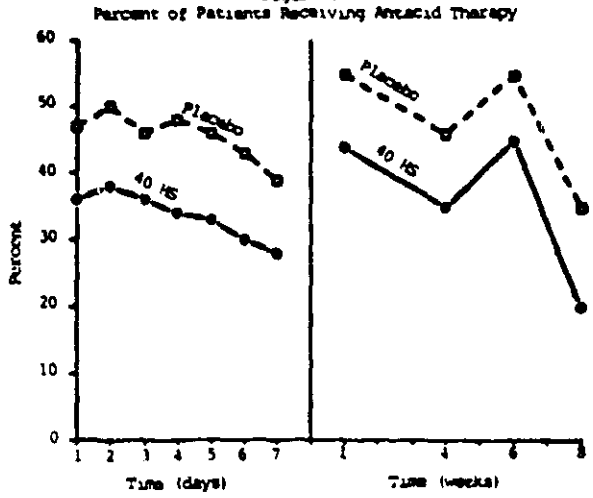

TABLE 55
Antacid Consumption
Mean Days of Antacid Therapy, Mean ± Standard Deviation

	Famotidine 40 HS			Placebo			Number of Days Difference Between 40 HS and Placebo
WEEK	N	MEAN		N	MEAN		
1	149	2.4	± 3.0*	145	3.2	± 3.2	-0.8
4	142	1.7	± 2.8*	137	2.7	± 3.2	-1.0
6	135	1.4	± 2.6*	129	2.1	± 3.0	-0.7
8	36	1.4	± 2.7*	48	2.2	± 3.2	-0.8

*Significantly different from the placebo group ($p \leq 0.05$).

(d) Patients global assessments (table 56): a remarkable observation is that good to excellent relief of symptoms at 4, 6 and 8 weeks respectively was reported by 64%, 70% and 74% of patients receiving placebo treatment. Nevertheless, an equal degree of symptomatic relief was reported in a sufficiently higher number of individuals receiving famotidine that the results with the drug were statistically significantly better than with placebo.

TABLE 56

Patients Global Assessments

TIMEPOINT	ASSESSMENT	FAMOTIDINE		PLACEBO	
		#	%	#	%
Week 4	Excellent/Good	105	80	85	64
	Fair/Poor/None	28	20	48	36
	Total*	133		133	
Week 6	Excellent/Good	125	86	99	71
	Fair/Poor/None	20	14	41	29
	Total*	145		140	
Week 8	Excellent/Good	127	88	102	73
	Fair/Poor/None	18	12	38	27
	Total*	145		140	
All Patients Treated	Excellent/Good	141	87	111	70
	Fair/Poor/None	21	13	47	30
	Total*	162		158	

*Significantly better distribution for the famotidine group than for the placebo group ($p < 0.01$)

4. Study No. 746

a. Title of study: Comparison of famotidine vs Gefarnate in the short-term treatment of benign gastric ulcer.

[Gefarnate is a long-chain unsaturated fatty acid marketed in Japan, among other countries, for the treatment of gastric ulcer. In the sponsor's opinion it is tantamount to a placebo.]

b. Design of study: in this multi-center, double-blind, randomized, active control trial patients with endoscopic evidence of a single-gastric ulcer, circular or oval in shape, were assigned to receive either famotidine 20 mg b.i.d. or Gefarnate 100 mg t.i.d. Matching placebos were taken at appropriate times utilizing a double-dummy technique. Antacid was supplied for relief of ulcer pain as necessary. Each dose was equivalent to 0.6 gm of dried aluminum hydoxide gel and the frequency of dosing was limited to 10 times per week.

Exclusion criteria included ulcers of the pyloric channel and esophagogastric junction, a history of gastric surgery (including vagotomy), nursing, confirmed or suspected pregnancy, or severe concurrent disease.

Baseline evaluation consisted of history, physical examination, laboratory studies, gastric endoscopy and biopsy. Physical examination and laboratory studies were repeated at weeks 4 and 8.

Healing was defined as complete epithelization, regardless of associated gastritis or erosions.

c. Investigators (vestigators at 32 Japanese centers participated.

Table 57

Country/Name	Affiliation	Location
Japan		
Yachi, Akira	Internist	Sapporo Medical College, Sapporo, Hokkaido
Ishimori, Akira	Gastroenterologist	Tohoku University, Sendai-shi, Miyagi Pref.
Sekiguchi, Toshikazu	Internist	Gunma University, Maebashi-shi, Gunma Pref.
Sakita, Takao	Internist	The University of Tsukuba, Tokyo Mihori-Gun, Ibaraki Pref.
Kitamura, Tatsuya	Internist	University of Tokyo, Bunkyo-ku, Tokyo
Takeuchi, Tadashi	Gastroenterologist	Tokyo Women's Medical Coll., Shinjuku-ku, Tokyo
Omata, Shozo	Gastroenterologist	Yokohama Shimin Hospital, Hodogaya-ku, Kanagawa Pref.
Honda, Toshio	Internist	Nihon University, Kanda Chiyoda-ku, Tokyo
Umeda, Moritsugu	Gastroenterologist	Nat'l Medical Center Hosp., Shinjuku-ku, Tokyo
Hongo, Hoshio	Internist	Icho Hospital, Shinjuku-ku, Tokyo
Kubota, Yuzuru	Internist	St. Luke's Int'l Hospital, Chuo-ku, Tokyo
Takasu, Sachio	Gastroenterologist	Kanto Teishin Hospital, Shinagawa-ku, Tokyo
Tsuchiya, Masahara	Gastroenterologist	Keio University, Shinjuku-ku, Tokyo
Sugata, Fumio	Gastroenterologist	Showa University, Yokohama, Kanagawa Pref.
Okabe, Haruya	Internist	Kitasato University, Sagamihara-shi, Kanagawa Pref.
Hisa, Takeshi	Internist	Tokai University, Isehara-shi, Kanagawa Pref.
Okabe, Kazuhiko	Gastroenterologist	St. Marianna University, Kawasaki-shi, Kanagawa Pref.
Watanabe, Yozo	Surgeon	Juntendo University, Bunkyo-ku, Tokyo
Kaneko, Eizo	Internist	Hamamatsu University, Hamamatsu-shi, Shizuoka Pref.
Nakazawa, Saburo	Internist	Nagoya University, Nagoya, Aichi Pref.
Takeuchi, Toshihiko	Internist	Nagoya City University, Nagoya, Aichi Pref.
Suyama, Tetsuji	Gastroenterologist	The Ctr. for Adult Diseases, Moriyama-shi, Shiga Pref.
Uchima, Haruto	Internist	Kyoto University, Kyoto-shi, Kyoto
Kawai, Keiichi	Internist	Kyoto Prefectural University, Kyoto-shi, Kyoto
Yukawa, Eiyo	Gastroenterologist	Yukawa Icho Hospital, Tennoji-ku, Kyoto
Shimoyama, Takeshi	Internist	Hyogo College of Medicine, Nishinomiya, Hyogo Pref.
Kita, Shoichi	Internist	Kawasaki Medical College, Okayama-shi, Okayama Pref.
Ohe, Keiji	Internist	Hiroshima University, Hiroshima-shi, Hiroshima Pref.
Mori, Hiroyoshi	Gastroenterologist	University of Tokushima, Tokushima-shi, Tokushima Pref.
Misawa, Tadashi	Internist	Kyushu University, Fukuoka-shi, Fukuoka Pref.
Inoue, Hikio	Internist	Fukuoka University, Fukuoka-shi, Fukuoka Pref.
Yunoki, Kazuo	Internist	Kagoshima University, Kagoshima-shi, Kagoshima Pref.

d. Results

(1) Comparability of treatment groups (table 58): there were 96 patients in each group; the 2 groups were comparable in all essential respects.

(2) Exclusions from analysis of effectiveness (table 59): almost all of the 23% of patients lost to analysis were a result of failure to start therapy within [illegible] of the baseline endoscopy; this left for analysis 72 patients in the famotidine group, 75 in the Gefarnate group.

(3) Safety

(a) Vital signs: drug had any effect on vital signs.

TABLE 59

[illegible] from Analysis of Effectiveness

	Famotidine 20 BID	Gefarnate 100 TID
[illegible]	1	1
[illegible]tant Drug	1	1
[illegible]copy missing	22	19
[illegible] out of range		
TOTAL	24 (25%)	21 (22%)

TABLE 60

Effect of Treatment on Vital Signs (means)

VARIABLE	TREATMENT	N	BASELINE	ENDPOINT	CHANGE FROM BASELINE
Body weight (kg)	Famotidine 20 BID	28	72.6	72.0	-0.4
	Gefarnate 100 TID	29	72.4	70.2	-2.2
Pulse (beats/min)	Famotidine 20 BID	23	55.6	56.2	+0.6
	Gefarnate 100 TID	24	55.0	55.6	+0.6
Systolic BP (mmHg)	Famotidine 20 BID	46	122.3	122.8	+0.5
	Gefarnate 100 TID	46	122.2	120.4	-1.8
Diastolic BP (mmHg)	Famotidine 20 BID	46	76.7	75.0	-0.7
	Gefarnate 100 TID	46	75.3	73.8	-1.5

(b) Clinical adverse experiences: drug-related adverse symptoms occurred in 5 patients receiving famotidine, 17 receiving Gefarnate (table 61). The most commonly reported adverse symptoms were constipation, occurring in 4 (4.2%) of the patients and nausea, occurring in 2 (2.1%) in each group. Two serious clinical adverse experiences occurred in each of the treatment groups, gastric cancer and a cerebral vascular accident in the famotidine group, gastric cancer and gastrointestinal bleeding in the Gefarnate group. Of these, only the case of hemorrhage was considered possibly drug-related. Two patients in addition to these, both receiving Gefarnate, were withdrawn because of adverse experiences (table 62), one because of diarrhea/nausea, the other because of weight loss, both considered possibly/probably drug-related.

TABLE 61

Drug-Related* Clinical Adverse Experience

ADVERSE EXPERIENCE	FAMOTIDINE		GEFARNATE	
Body as a Whole	0		0	
Abdominal Pain		0		1
Digestive System	5		15	
Anorexia		0		4
Constipation		3		3
Diarrhea		1		3
Eructation		0		2
Flatulence		1		2
Gastrointestinal Hemorrhage		0		1
Heartburn		0		2
Nausea		2		2
Vomiting		1		0
Peptic Ulcer		0		1
Metabolic/Nutritional System	0		1	
Weight Loss		0		1

*"Possibly", Probably" or "Definitely" related to test drug in investigator's opinion. Total numbers represent counts of patients, not counts of adverse experiences.

TABLE 62

Patients withdrawn Due to Adverse Experience

TREATMENT	NO.	ADVERSE EXPERIENCE	INTENSITY	DRUG RELATIONSHIP POSS/PROB
Famotidine (n=96)	103	Stomach Cancer	Severe	Definitely Not
	424	CVA	Severe	Probably Not[a] 1
Gefarnate (n=96)	102	Gastrointestinal bleeding	Severe	Possibly
	211[b]	Diarrhea/Nausea	Moderate	Possibly
	262[b]	Weight Loss	Severe	Probably
	292	Gastric Cancer	Severe	Definitely Not 3

a "Probably not" = "Possibly"
b Also considered protocol violators

(c) Laboratory adverse events: 15 patients receiving famotidine and 14 receiving Gefarnate were found to have abnormal laboratory values; none resulted in withdrawal from the trial. Of the 2 events considered drug-related, one patient on famotidine developed thrombocytopenia (probably not drug-related) and one on Gefarnate had a drop in hemoglobin and red cell count.

TABLE 63

Cumulative number healed/number evaluable (%)

Week	Endoscopic range, days	Famotidine n=72	Gefarnate n=75	p
4	Up to 32	19 (26)	3 (4)	0.01
8	33 to 60	46 (64)	18 (24)	0.01
Later	61 to 124	54 (75)	23 (31)	0.01

[illegible]: at all 3
weeks and
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f healing
with
t an impressive record for famotidine
ealing at 8 weeks, 46/72 (64%), was
pean multi-center trial. However,
se patients in Hawaii, gastric ulcer
than in occidentals.

(b) Relief of pain (figure 45): the percentage of patients relieved of pain was statistically significantly higher in patients receiving famotidine at the end of 1 week (2-8 days), 2 weeks (9-15 days) and 4 weeks (16-32 days). Thereafter the percentage of patients relieved of pain was approximately 90% with both treatments.

(c) Antacid consumption (figure 46): during the first 4 weeks the percentage of patients taking antacids was far less in patients receiving famotidine. After 4 weeks none of the patients receiving famotidine were taking antacids, while 10-20% of those receiving Gefarnate were continuing to do so.

Figure 45
Percentage of Patients With No Pain

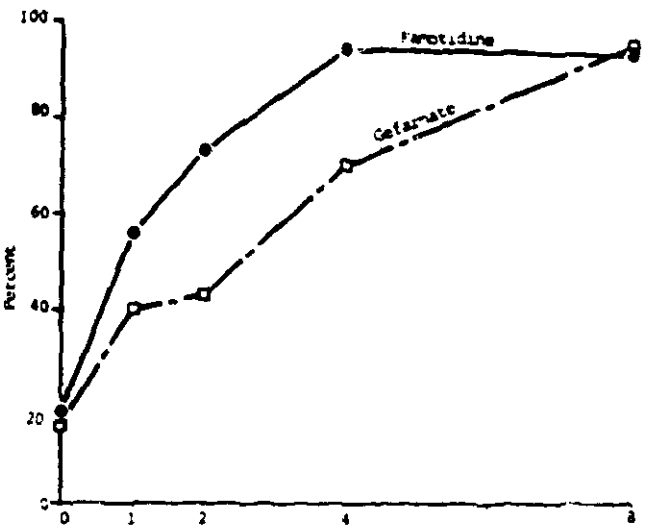
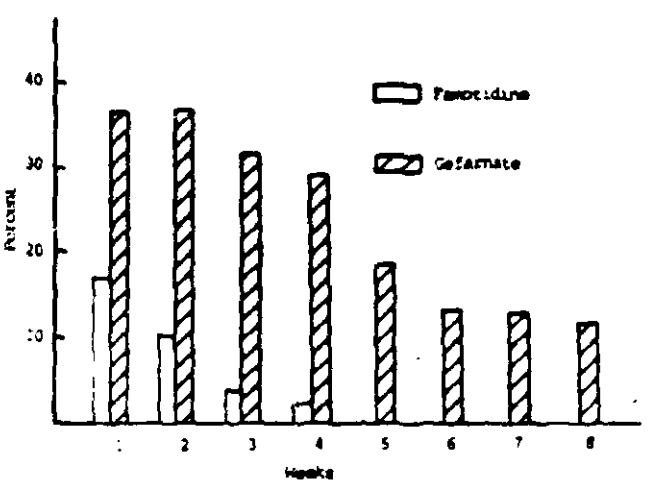


Figure 46
Percentage of Patients Taking Antacid



(d) Investigators' global evaluations (table 64): the data show that the incidence of symptomatic relief greatly exceeds the incidence of healing, confirming what has long been an article of faith in the annals of peptic ulcer disease.

TABLE 64

Investigators' Global Evaluation

Cumulative number markedly improved/number evaluable (%)

Marked improvement	Famotidine	Gefarnate	p
Week 4	55/76 (72)	17/80 (21)	0.01
Week 8	65/77 (84)	31/79 (39)	0.01

IV. Summary of NDA 19-462

A. Clinical pharmacology: famotidine was well-tolerated in volunteer subjects in doses at least twice the oral and intravenous recommended therapeutic doses. No serious adverse events, either in the form of symptoms or laboratory value deviations were encountered. Bioavailability was in the range of 40-45%. The half-life of the drug was of the order of 3 hours. Famotidine administered orally suppressed pentagastrin-stimulated gastric acid secretion in a dose-related fashion. The acid inhibiting effect of famotidine 5 mg was equivalent to that of cimetidine 300 mg. Twelve hours after administration of famotidine 20 mg, inhibition of pentagastrin-stimulated acid ranged from 18 to 88% with a mean of 54%. Doses of 20 or 40 mg b.i.d. suppressed nocturnal acid secretion more than

(b) Relief of pain (figure 45): the percentage of patients relieved of pain was statistically significantly higher in patients receiving famotidine at the end of 1 week (2-8 days), 2 weeks (9-15 days) and 4 weeks (16-32 days). Thereafter the percentage of patients relieved of pain was approximately 90% with both treatments.

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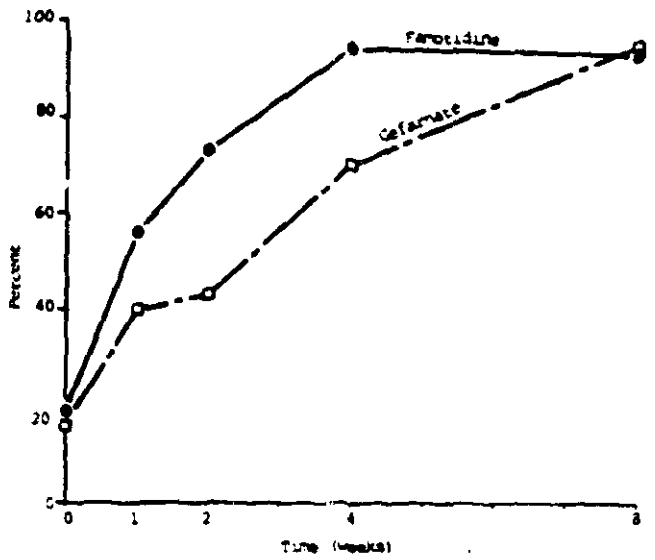

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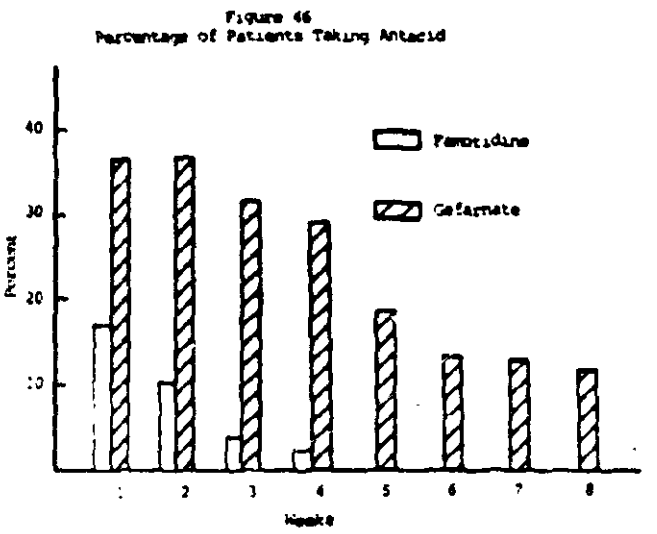

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90% and meal-stimulated secretions an average of 41% and 57% respectively. A single-dose of 40 mg at bedtime inhibited nocturnal acid secretion, with a carryover effect on the acid response the next morning's breakfast meal. No cumulative effect was observed when famotidine was given over a period of 5 days. Doses of 20 or 40 mg given at bedtime inhibited breakfast, but not lunch- or dinner-stimulated acid secretion. An additional dose given following breakfast did reduce the acid response to the noon meal. The results of these tests of the effect of famotidine on acid secretion were the basis of the decision to include doses of 40 mg h.s., 20 mg b.i.d. and 40 mg b.i.d. in clinical trials of healing of duodenal ulcer.

Blood levels of prolactin, FSH, LH, and testosterone were not altered by administration of famotidine; there was a slight increase in serum gastrin. In a study designed to evaluate the effect of famotidine on hepatic metabolic function, famotidine did not induce changes in elimination of aminopyrine or antipyrine in most subjects. The significance of this observation was tested in drug-interaction studies, the results of which indicated that famotidine does not alter the pharmacokinetics of theophylline, warfarin, phenytoin or diazepam.

B. Effectiveness

1. Short-term treatment of duodenal ulcer

a. Incidence of healing: 2 multi-center trials evaluated the incidence of healing with 3 dosage regimens of famotidine (40 mg h.s., 20 mg b.i.d., and 40 mg b.i.d.) one a United States trial comparing famotidine with placebo, the other an International trial comparing famotidine with ranitidine. In both trials the patients were endoscoped at 2, 4 and 8 weeks, the last endoscopy being at the first interval of healing, i.e. in the analysis of the cumulative incidence of healing, a patient whose ulcer was found to be healed at 2 weeks was considered to be healed at 8 weeks. The patients were given diary cards for recording episodes of pain and number of doses taken. In the United States trial 34 investigators entered a total of 384 patients approximately equally distributed among the 4 treatment groups. All of the doses of famotidine were

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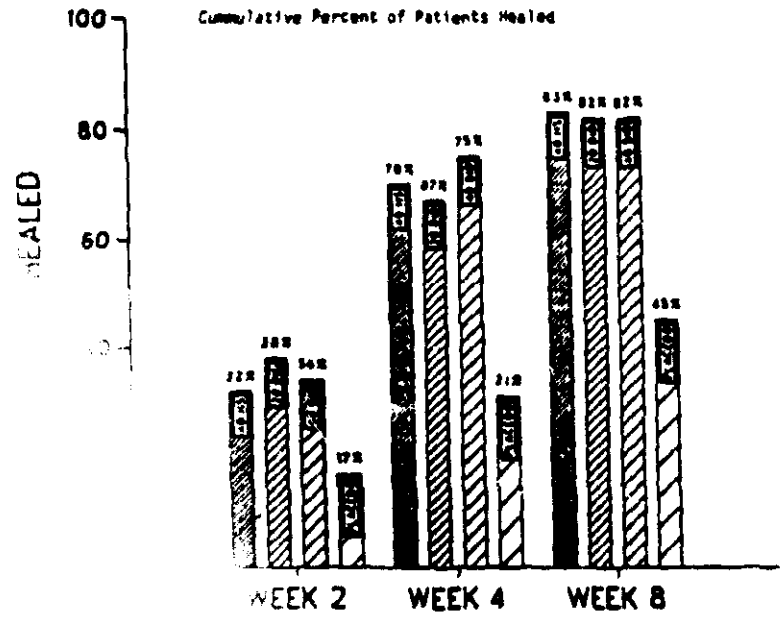
s.

Figure 47
Cumulative Percent of Patients Healed



incidence of healing (figure 48) with famotidine 40 mg h.s. at 4 weeks (68%) was less than that with ranitidine 150 mg b.i.d. (76%) but at 8 weeks they were equal (87% vs 90%). Comparing the results of the U.S. and International trials (table 65) the incidence of healing was the same with the dose of 40 mg h.s., but with the b.i.d. doses the incidence of healing was higher in the International trial at both 4 and 8 weeks.

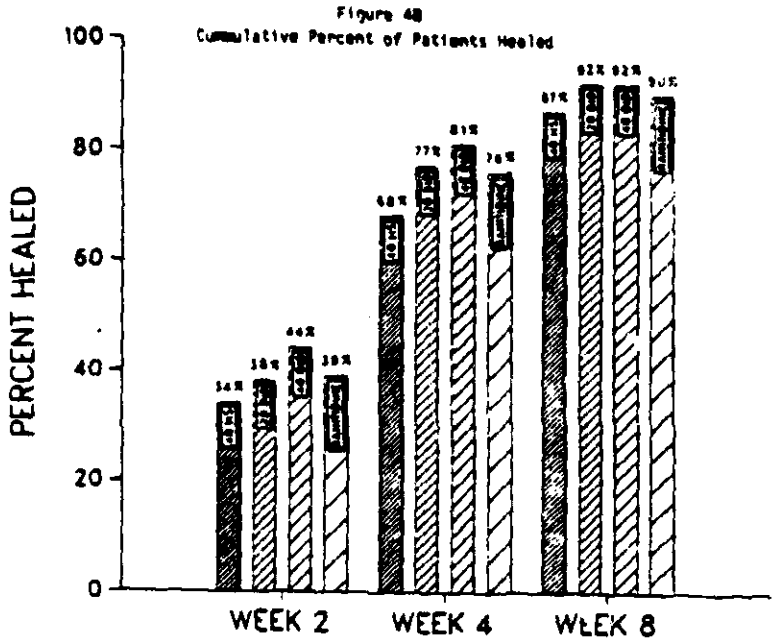
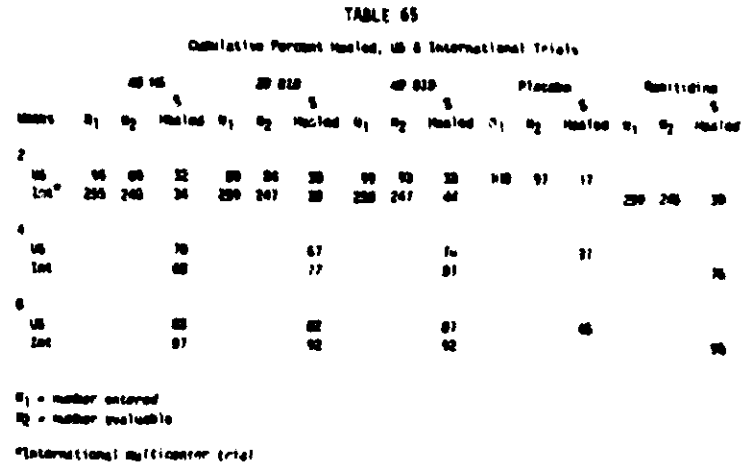


TABLE 65

Cumulative Percent Healed, US & International Trials



n_1 = number entered
n_2 = number evaluable

*International multicenter trial

b. Relief of pain: ulcer pain was relieved sooner and in a higher percentage of patients receiving famotidine than in those receiving placebo. When compared with ranitidine, pain relief with famotidine was not significantly different.

c. Antacid consumption: in the U.S. study the number of days on which antacids were taken, the number of antacid tablets taken and the percentage of patients taking antacids all favored famotidine over placebo by statistical analysis, but the differences were not clinically meaningful.

2. Prevention of recurrence of duodenal ulcer: the role of famotidine in the prevention of recurrence of duodenal ulcer was evaluated in 2 multicenter, placebo-controlled trials in patients whose ulcers had healed during the short-term treatment were eligible for admission to a trial of famotidine vs placebo in the prevention of recurrence of ulcer. In the U.S. trial 26 investigators entered 177 patients, 54 on 40 mg h.s., 57 on 20 mg h.s. and 66 on placebo. The incidence of recurrence at all intervals up to 6 months (figure 49), which was the cutoff time for analysis of the data, was significantly lower with famotidine. At 6 months the incidence with 40 mg h.s. was 30%, with 20mg h.s. 26%, with placebo 70%. The incidence of recurrence with 20 mg h.s. was not statistically significantly different from that with 40 mg h.s. In the International trial, 64 investigators entered 471 patients, 237 on 20 mg h.s. and 234 on placebo. The incidence of recurrence (figure 50) on both placebo and famotidine was similar to that in the U.S. trial. Thus, in both trials, the recommended dose of famotidine for prevention of recurrence (20 mg h.s.) was statistically significantly superior to placebo (Table 66).

Figure 49
Cumulative Incidence of Relapse (%)

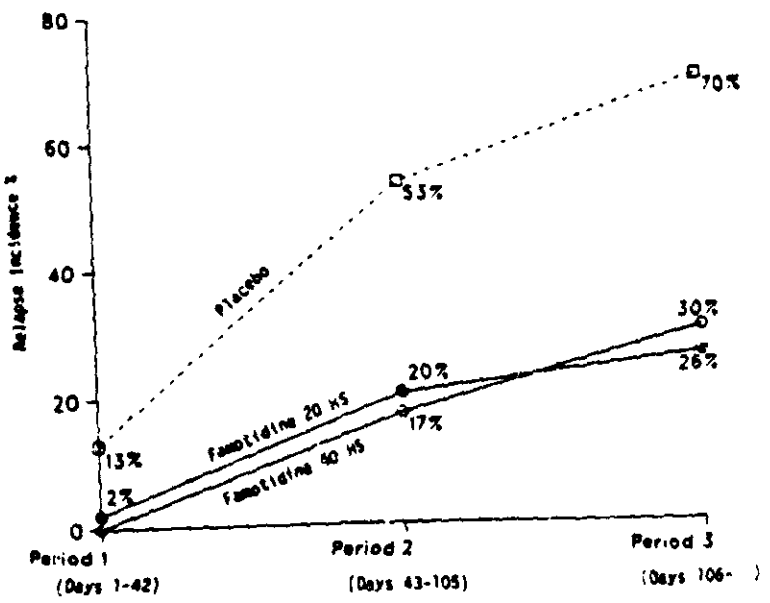


Figure 50
Cumulative Incidence of Relapse (%)

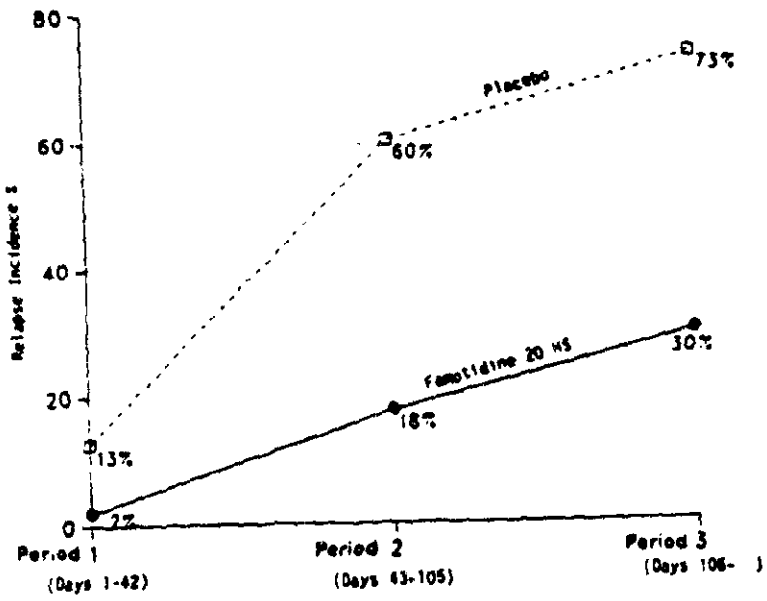


TABLE 66

Cumulative Life-Table Incidence of Recurrence (%)
U.S. and International Trials

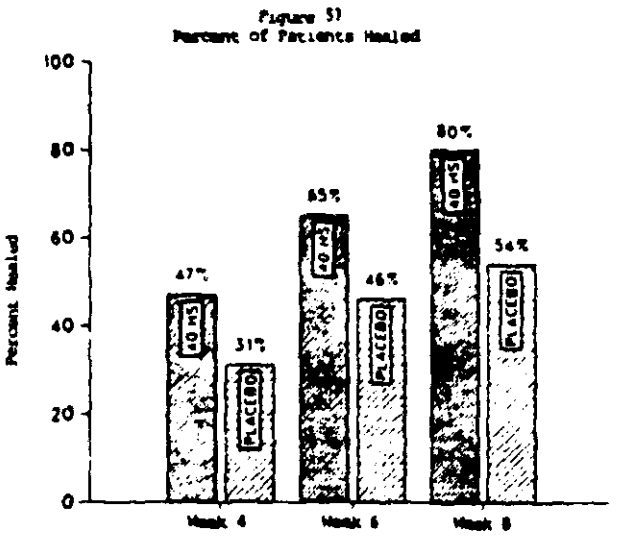
	40 HS n	40 HS % Recurred	20 HS n	20 HS % Recurred	Placebo n	Placebo % Recurred	p
Days 1-42							
U.S.	54	0	57	1.8	66	12.1	40 HS: <0.01; 20 HS: <0.05; PLA: <0.01
International			268	1.9	306	12.7	
Days 43-105							
U.S.	46	15.2	49	11.8	47	51.4	40 HS: <0.01; 20 HS: <0.01; PLA: <0.01
International			237	17.6	234	60.1	
Days 106 or later							
U.S.	22	30.6	32	25.5	10	66.7	40 HS: <0.01; 20 HS: <0.01; PLA: <0.01
International			182	29.4	95	73.1	

3. Treatment of gastric hypersecretory conditions: two studies were conducted in the United States on small series of patients with gastric acid secretion in the pathological range, all with suspected or proven Zollinger-Ellison syndrome. These patients had previously been treated with either cimetidine or ranitidine or both. The mean minimum daily doses expressed as grams/day required to suppress gastric acid secretion to less than 10 mEq/h during the 6 hours after administration of the drugs were famotidine 0.24, ranitidine 2.1 and cimetidine 7.8. Besides greater potency famotidine also had a longer duration of action than either of the other two H_2-blockers. Like ranitidine, but in contrast to cimetidine, famotidine was not associated with anti-androgenic side-effects. There is as yet no evidence that the higher potency and longer duration of action of famotidine will translate into dosage intervals less than 6 hours for adequate control of the gastric acid output.

4. Short-term treatment of gastric ulcer:

a. International multi-center trial: the only placebo controlled trial of famotidine in the short-term treatment of gastric ulcer was conducted in 14 countries with the participation of 44 investigators. A total of 336 patients were entered, 167 on famotidine 40 mg h.s., 169 on placebo.

(1) Incidence of healing: the proportion of patients whose ulcers healed was statistically significantly greater at all time intervals (4, 6 and 8 weeks) in patients receiving famotidine than in those receiving placebo (p 0.01)(figure 51). The incidence of healing with famotidine at the respective intervals was 47%, 65% and 80% in contrast to the respective percentages of 31, 46 and 54 with placebo.

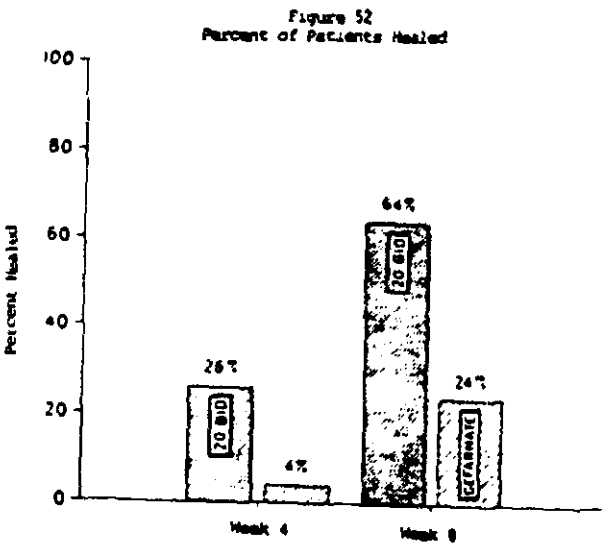


(2) Relief of pain: both day and night pain were more rapidly relieved in patients receiving famotidine.

(3) Antacid consumption: concomitant use of antacids was statistically significantly lower for patients treated with famotidine, but the difference was not enough to be of clinical importance.

(4) Patients' assessment of global response: at all time points patients in both groups claimed good to excellent symptomatic response in statistically significantly higher proportions than those who rated their responses as fair, poor or none, and in significantly higher proportions in patients receiving famotidine than in those receiving placebo.

2. Japanese clinical trial: the procedure was essentially the same as that in the International multi-center study except that the comparison was between famotidine 20 mg b.i.d. and Gefarnate 100 mg t.i.d. Investigators from 32 centers in Japan contributed a total 192 patients, 96 in each of the treatment groups. The incidence of healing of the gastric ulcers (figure 52) was much lower in the patients receiving famotidine than was the case in the International multi-center trial, possibly because the dosage of famotidine used in this trial (20 mg b.i.d.) is not comparable to that in the International trial (40 mg h.s.) and possibly because in the Japanese population gastric ulcer is a more resistant disease. The incidence of healing with famotidine vs Gefarnate was 26% vs 4% at 4 weeks and 64% vs 24% at 8 weeks.



The percentage of patients without pain was statistically significantly higher at all time points up to, but not including, 8 weeks in patients receiving famotidine. The percentage of patients taking antacids was significantly less with famotidine than with Gefarnate. Antacids were not required after the 4th week in patients on famotidine, but continued to be required in approximately 15% of patients taking Gefarnate up to 8 weeks.

V. Safety

Safety data updated to November 18, 1985 were available from 2,333 patients in world-wide trials. The most common clinical adverse experiences are headache (4.7%), diarrhea (1.7%), nausea (1.5%), constipation (1.3%) and dizziness (1.2%). The laboratory data indicate no evidence of serious drug-related hematological, hepatic or renal toxicity. The safety profile of famotidine will only become apparent, however, in the market place.

There were 19 deaths in the world-wide experience, none of them drug-related (table 67), only 3 of which occurred in patients treated for indications addressed in this NDA.

TABLE 67

Deaths in Patients Treated with famotidine

Ident.	Age	Sex	Immediate Cause	Concurrent Condition	Route of Administration	Indication
				JAPAN		
Japan	24	M	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
Japan	41	M	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
Japan	44	F	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
Japan	55	M	Hepatic failure	GI hemorrhage fulminant hepatitis	I.V.	stress ulcer
Japan	68	M	Hepatic failure	GI hemorrhage/ fulminant hepatitis	I.V.	stress ulcer
2103	Unk*	Unk	Unknown	GI bleeding/stress ulcer; Colon cancer	I.V.	stress ulcer
2104	Unk	Unk	MI**; Renal failure	GI hemorrhage/stress ulcer; MI (past)	I.V.	stress ulcer
2105	Unk	Unk	Respiratory failure	GI hemorrhage/stress ulcer; Colon cancer Renal insufficiency	I.V.	stress ulcer
0704	Unk	Unk	Unknown	GI hemorrhage/stress ulcer; Perforation of stomach; Rheumatoid arthritis	I.V.	stress ulcer
2501	72	M	Hepatic failure	GI hemorrhage/stress ulcer; Hepatoma; Subphrenic abscess	I.V.	stress ulcer
2702	58	M	Hepatic failure	GI hemorrhage/stress ulcer; Pancreatitis; Liver cancer; Cirrhosis; Cholelithiasis	I.V.	stress ulcer
3602	62	M	Unknown	GI hemorrhage/stress ulcer; Bladder cancer	I.V.	stress ulcer
				INTERNATIONAL		
1895	71	M	Myocardial Infarction	—	oral	maintenance therapy
718	44	M	Peritinitis	Cirrhosis of liver	I.V.	stress ulcer
20005	86	F	Respiratory failure	Pneumonia	oral	peptic ulcer
709	46	F	Septicemia	Third degree burns on 60% of body; pneumonia	I.V.	stress ulcer
718	23	M	Brain infarctions	—	I.V.	stress ulcer
709	75	F	Abdominal infection	Volvulus of small bowel with necrosis	I.V.	stress ulcer
				U. S.		
3	64	F	"Natural"	—	oral	Zollinger-Ellison Syndrome

*Unk = Unknown
**MI = Myocardial infarction

VI. Package insert: the insert (attached) is generally factually correct but is unnecessarily repetitive. I have indicated my suggestions for revision.

VII Conclusions

A. Pepcid (famotidine) is safe and effective in the following dosage for the following indications:

1. 40 mg h.s. for the short-term (4-8 weeks) treatment of duodenal ulcer.

2. 40 mg h.s. for the short-term (4-8 weeks) treatment of gastric ulcer.

3. 20 mg q 6h initially and increased as necessary to reduce gastric acid output below 10 mEq/hr in the treatment of Zollinger-Ellison syndrome.

B. Data from 2 6-month trials of prevention of recurrence of duodenal ulcer show that famotidine is more effective than placebo but do not provide a sufficiently long follow-up (at least one year) to permit a final assessment of the effectiveness of famotidine for this indication.

VIII Recommendations: Approve the application for the following indications and dosages:

1. 40 mg h.s. in the short-term (4-8 weeks) treatment of duodenal ulcer.

2. 40 mg h.s. in the short-term (4-8 weeks) treatment of gastric ulcer.

3. 20 mg q 6 h, increased as necessary to keep gastric acid output below 10 mEq/hr in the treatment of Zollinger-Ellison syndrome.

William H. Bachrach

William H. Bachrach, M.D.

cc: Orig. NDA 19-462
HFN-110
[redacted]
HFN-110/WHBachrach
rq:12-21-85:12-26:12-30:0409r

A.H.F.S. Category: 56:40

MSD| Tablets PEPCID™ XXXXXXX
(Famotidine, MSD)

PEPCID™
(Famotidine, MSD)

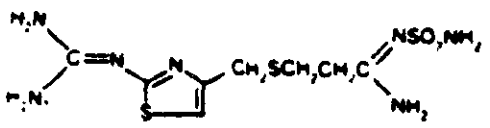
DESCRIPTION[1]

1. Chemistry, Manufacturing and Controls
**Item II. D. 1. Vol. 1.1, p. 25
Item III. A. 8. Vol. 1.2, p. 08

The active ingredient in Tablets PEPCID* (Famotidine, MSD), is a histamine H_2 receptor antagonist.

Famotidine is 3-[[[2- [(aminoiminomethyl) amino]-4-thiazoyl] methyl]thio]-N-(aminosulfonyl) -propanimidamide.

The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.43. Its structural formula is:



Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc, titanium dioxide.

* Trademark of MERCK & CO., INC.

** All annotations will have two references. The first reference is to Item II-Summary of Application contained in this volume. The page number indicates where a brief description can be found. The second reference is to a specific technical section and gives the volume and page number where a detailed description can be found.

PEPCID™
(Famotidine, MSD)

CLINICAL PHARMACOLOGY

GI Effects: PEPCID is a competitive inhibitor of histamine H_2-receptors.[2] The primary clinically important pharmacologic activity of PEPCID is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by PEPCID,[3] while changes in pepsin secretion are proportional to volume output.[4]

In both normal volunteers and hypersecretors, PEPCID inhibited basal, nocturnal[3,7] and daytime gastric secretion,[3,5] as well as secretion stimulated by ~~a variety of stimuli, such as~~ pentagastrin[4,6,8] ~~and food.[3,7]~~

After oral administration, the onset of the antisecretory effect occurred within one hour;[3,4,5,7] the maximum effect was dose-dependent, occurring within one to three hours.[3,4,6] Duration of inhibition of secretion was 10 to 12 hours.[3,7] After intravenous administration, the maximum effect was achieved within 30 minutes.[8] Single oral doses of 20 and 40 mg inhibited basal, 2nd nocturnal acid secretion in all subjects; mean gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours.[3] Similar doses given in the morning

2. Preclinical Pharmacology
   Item II. D. 2. Vol. 1.1, p. 29
   Item IV. A. 1. Vol. 1.3, p. 01

3. Ryan Study No. 8
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1819

4. Smith Study No. 2
   Item II. D. 4. Vol. 1.1, p. 87
   Item VII. F. 1. a. ii. Vol. 1.31, p. 1518

5. Ryan Study No. 7
   Item II. D. 4. Vol. 1.1, p. 88
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1748

6. McCallum Study No. 3
   Item II. D. 4. Vol. 1.1, p. 87
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1583

7. Cohen Study No. 5
   Item II. D. 4. Vol. 1.1, p. 88
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1668

8. Hunt Study No. 725
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1917

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CLINICAL PHARMACOLOGY (cont'd)

suppressed food-stimulated acid secretion in all subjects, with mean suppression of 76% and 84%, respectively, 3 to 5 hours after drug, and of 25% and 30%, respectively, 8 to 10 hours after drug; however, in some subjects who received the 20 mg dose, the antisecretory effect was dissipated earlier, within 6-8 hours.[9] There was no cumulative effect with repeated doses.[10] The basal nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of PEPCID to mean values of 5.0 and 6.4, respectively.[9,11] When PEPCID was given in the morning, the ~~basal~~ daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of PEPCID was raised to about 5.0.[9,11]

Fasting or postprandial serum gastrin levels may be slightly elevated during periods of drug antisecretory effect,[12,13] and with chronic therapy, an increase in gastric bacterial flora may occur.[14] Gastric emptying and exocrine pancreatic function are not affected by PEPCID.[15]

9. Ryan Study No. 8
   Item II. D. 4. Vol. 1.1, p. 89
   Item VII. F. 1. a. ii. Vol. 1.32, p. 1819

10. Ryan Study No. 7
    Item II. D. 4. Vol. 1.1, p. 88
    Item VII. F. 1. a. ii. Vol. 1.32, p. 1748

11. Smith Study No. 51
    Item II. D. 4. Vol. 1.1, p. 89
    Item VII. F. 1. a. ii. Vol. 1.33, p. 1975

12. Zinny Study No. 1
    Item II. D. 4. Vol. 1.1, p. 91
    Item VII. F. 1. a. i. Vol. 1.30, p. 1050

13. Smith Study No. 2
    Item II. D. 4. Vol. 1.1, p. 87
    Item VII. F. 1. a. ii. Vol. 1.31, p. 1518

14. Cattau Study No. 12
    Item II. D. 4. Vol. 1.1, p. 92
    Item VII. F. 1. a. iii. Vol. 1.33, p. 2101

15. Redinger Study No. 61
    Item II. D. 4. Vol. 1.1, p. 92
    Item VII. F. 1. a. iii. Vol. 1.33, p. 2036

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Other effects: Systemic pharmacologic effects of PEPCID in the CNS, cardiovascular, respiratory or endocrine systems have not been found to date.[16,22,28] Serum prolactin levels do not rise after intravenous bolus doses of 20 mg PEPCID[17] and no antiandrogenic effects have been detected.[18,19]

Pharmacokinetics

PEPCID is incompletely absorbed.[17,21] The bioavailability of oral doses is 40-45%.[17] Bioavailability may be slightly increased by food, or slightly decreased by antacids;[20] however, these effects are of no clinical consequence. PEPCID undergoes minimal first-pass metabolism.[21] After oral doses, peak plasma levels occur in 1-3 hours.[17,21,22] Plasma levels after multiple doses are similar to those after single doses.[23,25] Fifteen to 20% of PEPCID in plasma is protein bound.[24] PEPCID has an elimination half-life of 2.5-3.5 hours.[17,22,28] PEPCID is eliminated by renal (65-70%)[17] and metabolic (30-35%) routes.[17,21] Renal clearance is 250-450 mL/min., indicating some tubular excretion.[17,22,28]

16. Shrivastava Study No. 31
Item II. D. 4. Vol. 1.1, p. 91
Item VII. F. 1. a. iii. Vol. 1.33, p. 2193

17. Williams Study No. 42
Item II. D. 3. Vol. 1.1, p. 52
Item V. M. 12. Vol. 1.22, p. 259

18. Jensen Study No. 6
Item II. D. 4. Vol. 1.1, p. 127
Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

19. Cohen Study No. 41
Item II. D. 4. Vol. 1.1, p. 129
Item VII. F. 2. a. iii. Vol. 1.38, p. 4136

20. Kann Study No. 47
Item II. D. 3. Vol. 1.1, p. 76
Item V. M. 24. Vol. 1.25, p. 1316

21. Rotmensch Study No. 40
Item II. D. 3. Vol. 1.1, p. 64
Item V. M. 19. Vol. 1.23, p. 776

22. Zinny Study No. 1
Item II. D. 3. Vol. 1.1, p. 67
Item V. M. 20. Vol. 1.24, p. 843

23. De Schepper Study No. 748
Item II. D. 3. Vol. 1.1, p. 54
Item V. M. 15. Vol. 1.22, p. 388

24. Lin MSDRL Study
Item II. D. 3. Vol. 1.1, p. 72
Item V. M. 21. Vol. 1.24, p. 959

25. Williams Study No. 48
Item II. D. 3. Vol. 1. 1, p. 70
Item V. M. 25. Vol. 1.25, p. 1400

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Pharmacokinetics (cont'd)

Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound.[26,27] The only metabolite identified in man is the S-oxide.[28] There is a close relationship between creatinine clearance values and the elimination half-life of PEPCID.[29,30] In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min., PEPCID elimination half-lives may exceed 20 hours and adjustment of dosing intervals may be necessary[29] (see PRECAUTIONS, DOSAGE AND ADMINISTRATION). In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of PEPCID.[30]

26. Williams Study No. 42
    Item II. D. 3. — Vol. 1.1, p. 52
    Item V. M. 12. — Vol. 1.22, p. 259

27. Rotmensch Study No. 40
    Item II. D. 3. — Vol. 1.1, p. 64
    Item V. M. 19. — Vol. 1.23, p. 776

28. Yamada Yamanouchi Study
    Item II. D. 3. — Vol. 1.1, p. 67
    Item V. M. 8 — Vol. 1.22, p. 218

29. Abraham Study No. 404
    Item II. D. 3. — Vol. 1.1, p. 58
    Item V. M. 17 — Vol. 1.23, p. 639

30. Martin Study No. 744
    Item II. D. 3. — Vol. 1.1, p. 78
    Item V. M. 16 — Vol. 1.23, p. 450

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Clinical Studies

Duodenal Ulcer

In a U.S. multicenter, double-blind study[31] in outpatients with endoscopically confirmed duodenal ulcer, PEPCID ~~given as~~ 40 mg h.s. was compared to placebo. As shown in the table below, most patients treated with PEPCID were healed by Week 4.

31. U.S. Multicenter Trial vs. Placebo Acute Phase
Item II. D. 4. Vol. 1.1, p. 96
Item VII. F. 2. a. i. Vol. 1.35, p. 2922

Outpatients with endoscopically confirmed healed ulcers

	PEPCID 40 mg h.s. (N = 89)	Placebo h.s. (N = 97)
Week 2	*32 %	17 %
Week 4	*70 %	31 %

* statistically significantly different than placebo ($p < 0.001$)

Patients not healed by Week 4 were continued in the study. By Week 8, the incidence of healing ~~rate~~ was 83% for patients on therapy with PEPCID versus 45% for patients on placebo. The ~~rate~~ incidence of ulcer healing with PEPCID was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients on PEPCID than for patients on placebo; patients on PEPCID also took less antacid than the patients on placebo, but the difference was not clinically meaningful.

PEPCID™
(Famotidine, MSD)

Clinical Studies

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Item II. D. 4. Vol. 1.1, p. 96
Item VII. F. 2. a. i. Vol. 1.35, p. 2922

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In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients on PEPCID than for patients on placebo; patients on PEPCID also took less antacid than the patients on placebo, but the difference was not clinically meaningful.

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Long-Term Maintenance Treatment of Duodenal Ulcers

The efficacy of a dosage regimen of PEPCID, 20 mg h.s. in the prevention of duodenal ulcer recurrence was compared to placebo h.s. in a U.S. double-blind, multicenter study[32] of patients with endoscopically confirmed healed duodenal ulcers. Following 6 months of therapy, PEPCID was significantly more effective ($p < 0.01$) than placebo in preventing ulcer recurrence. Of the 49 patients who completed up to 24 weeks of therapy with PEPCID 20 mg h.s., 22% of patients on PEPCID experienced ulcer recurrence, as compared to 55% of 62 patients on placebo. In this clinical trial, patients have been maintained on this regimen for up to one year.

32. U.S. Multicenter Trial
vs. Placebo
Maintenance Phase
Item II. D. 4. Vol. 1.1, p. 108
Item VII. F. 2. a. i. Vol. 1.35, p. 2923

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Gastric Ulcer

In an international double-blind multicenter, study[33] in patients with endoscopically confirmed ~~acute benign~~ gastric ulcers, PEPCID, 40 mg h.s., was compared to placebo h.s. As illustrated in the table below, the incidence ~~rate~~ of ulcer healing with PEPCID was statistically significantly different than placebo, after 4 weeks to 8 weeks of therapy, based on proportion of endoscopically confirmed healed ulcers.

Patients with endoscopically confirmed healed ulcers

	PEPCID 40 mg h.s. (N = 149)	Placebo h.s. (N = 145)
Week 4	*47 %	31 %
Week 6	*65 %	46 %
Week 8	*80 %	54 %

* statistically significantly different than placebo ($p < 0.01$)

In this study, relief of daytime and nighttime pain was quicker for patients on therapy with PEPCID than for patients on placebo; patients on therapy with PEPCID also took antacids significantly less frequently than the patients on placebo, but the difference was not clinically meaningful.

33. International Multicenter Trial vs. Placebo
Item II. D. 4. Vol. 1.1, p. 117
Item VII. F. 2. a. ii. Vol. 1.37, p. 3615

PEPCID™
(Famotidine, MSD)

Gastric Ulcer

In an international double-blind multicenter, study[33] in patients with endoscopically confirmed ~~acute benign~~ gastric ulcers, PEPCID, 40 mg h.s., was compared to placebo h.s. As illustrated in the table below, the incidence ~~rate~~ of ulcer healing with PEPCID was statistically significantly different than placebo, after 4 weeks to 8 weeks of therapy, based on proportion of endoscopically confirmed healed ulcers.

	Patients with endoscopically confirmed healed ulcers	
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33. International Multicenter Trial vs. Placebo
Item II. D. 4. Vol. 1.1, p. 117
Item VII. F. 2. a. ii. Vol. 1.37, p. 3615

PEPCID™
(Famotidine, MSD)

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome) ~~Multiple Endocrine Adenomas)~~

In studies[34,35] of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome ~~and multiple endocrine adenomas,~~ PEPCID significantly inhibited gastric acid secretion and controlled associated symptoms. Doses from 20 ~~mg p.r.n. to~~ 160 mg q 6h maintained basal acid secretion below 10 mEq/hr.; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. PEPCID was well tolerated at these high dose levels for prolonged periods (greater than 12 months) and there were no cases reported of gynecomastia, increased prolactin levels, or impotence.

34. Jensen Study No. 6
    Item II. D. 4. Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

35. Cohen Study No. 41
    Item II. D. 4. Vol. 1.1, p. 129
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4136

PEPCID™
(Famotidine, MSD)

INDICATIONS AND USAGE

PEPCID is indicated in:

1. Treatment of acute duodenal ulcer.[36,37]

   Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 8 weeks.

2. Prophylactic use in duodenal ulcer disease[38,39]

3. Treatment of acute benign gastric ulcer.[40,41]

   Most patients heal within 8 weeks.

4. Treatment of ~~pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)~~.[42,43]

36. U.S. Multicenter Trial vs. Placebo Acute Phase
    Item II. D. 4. — Vol. 1.1, p. 96
    Item VII. F. 2. a. i. — Vol. 1.35, p. 2922

37. International Multicenter Trial vs. Ranitidine
    Item II. D. 4. — Vol. 1.1, p. 102
    Item VII. F. 2. a. i. — Vol. 1.36, p. 3283

38. U.S. Multicenter Trial vs. Placebo Maintenance Phase
    Item II. D. 4. — Vol. 1.1, p. 108
    Item VII. F. 2. a. i. — Vol. 1.35, p. 2923

39. International Multicenter Trial vs. Placebo
    Item II. D. 4. — Vol. 1.1, p. 113
    Item VII. F. 2. a. i. — Vol. 1.36, p. 3475

40. International Multicenter Trial vs. Placebo
    Item II. D. 4. — Vol. 1.1, p. 117
    Item VII. F. 2. a. ii. — Vol. 1.37, p. 3615

41. Yamanouchi Multicenter Trial vs. Gefarnate
    Item II. D. 4. — Vol. 1.1, p. 123
    Item VII. F. 2. a. ii. — Vol. 1.37, p. 3774

42. Jensen Study No. 6
    Item II. D. 4. — Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. — Vol. 1.38, p. 4028

43. Cohen Study No. 41
    Item II. D. 4. — Vol. 1.1, p. 129
    Item VII. F. 2. a. iii. — Vol. 1.38, p. 4136

PEPCID™
(Famotidine, MSD)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

PRECAUTIONS

General

Symptomatic response to therapy with PEPCID does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency

Dosing intervals may need to be prolonged in patients with severe renal insufficiency (creatinine clearance < 10 mL/min) to adjust for the longer elimination half-life of famotidine.[44] (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). However, no drug-related toxicity has been found with high plasma concentrations of famotidine.[45]

44. Abraham Study No. 404
Item II. D. 3. Vol. 1.1, p. 58
Item V. M. 17. Vol. 1.23, p. 639

45. Jensen Study No. 6
Item II. D. 4. Vol. 1.1, p. 127
Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

PEPCID™
(Famotidine, MSD)

Drug Interactions

No drug interactions have been identified. Studies with famotidine in man, in animal models,[46] and in vitro[47] have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man have included warfarin,[48] theophylline,[49] phenytoin,[50] diazepam,[51] aminopyrine[52] and antipyrine.[52] Indocyanine green as an index of hepatic blood flow and/or hepatic drug extraction has been tested and no significant effects have been found.[50]

46. Preclinical Pharmacology
    Item II D. 2. Vol. 1.1, p. 33
    Item IV. D. 2. (19) Vol. 1.5, p. 1232

47. Preclinical Pharmacology
    Item II D. 2. Vol. 1.1, p. 33
    Item IV D. 2. (20) Vol. 1.5, p. 1257

48. Ryan Study No. 53
    Item II D. 3. Vol. 1.1, p. 84
    Item VII. F. 1. a. iv. Vol. 1.34, p. 2725

49. Williams Study No. 48
    Item II D. 3. Vol. 1.1, p. 82
    Item VII. F. 1. a. iv. Vol. 1.34, p. 2375

50. Williams Study No. 55
    Item II D 3. Vol. 1.1, p. 83
    Item VII. F. 1. a. iv. Vol. 1.34, p. 2472

51. Zinny Study No. 58
    Item II D. 3. Vol. 1.1, p. 81
    Item VII. F. 1. a. iv. Vol. 1.33, p. 2284

52. Langman Study No. 690
    Item II D. 3. Vol. 1.1, p. 80
    Item VII. F. 1. a. iv. Vol. 1.33, p. 2201

PEPCID™
(Famotidine, MSD)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 106 week study[53] in rats and a 92 week study[54] in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the maximum recommended human dose), there was no evidence of carcinogenic potential for PEPCID.

Famotidine was negative in the microbial mutagen test (Ames test) using Salmonella typhimurium and Escherichia coli with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate.[55] In in vivo studies in mice with a micronucleus test[56] and a chromosomal aberration test[57], no evidence of a mutagenic effect was observed.

In studies with rats given oral doses[58] of up to 2000 mg/kg/day or intravenous doses[59] of up to 200 mg/kg/day (approximately 2500 and 250 times the maximum recommended human dose, respectively), fertility and reproductive performance were not affected.

53. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 41
Item IV. D. 6. (3). Vol. 1.19, p. 6510

54. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 41
Item IV. D. 6. (2). Vol. 1.18, p. 6113

55. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 40
Item IV. D. 5. (1). Vol. 1.17, p. 5817

56. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 40
Item IV. D. 5. (12). Vol. 1.17, p. 5972

57. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 40
Item IV. D. 5. (13). Vol. 1.17, p. 5985

58. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 37
Item IV. D. 4. (11). Vol. 1.15, p. 4997

59. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (12). Vol. 1.16, p. 5266

PEPCID™
(Famotidine, MSD)

Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats [60,61] and rabbits [62,63] at oral doses of up to 2000 and 500 mg/kg/day, respectively (approximately 2500 and 625 times the maximum recommended human dose, respectively), and have revealed no evidence of impaired fertility or harm to the fetus due to PEPCID. There are, however, no adequate or well-controlled studies in pregnant women.

Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies performed in lactating rats have shown that famotidine is secreted in breast milk.[64] It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from PEPCID, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

60. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 37
Item IV. D. 4. (1). Vol. 1.12, p. 4106

61. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (2). Vol. 1.13, p. 4144

62. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (5). Vol. 1.14, p. 4671

63. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (6). Vol. 1.15, p. 4753

64. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 33
Item IV. D. 2. (15). Vol. 1.5, p. 1187

PEPCID™
(Famotidine, MSD)

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

No dosage adjustment is required based on age[65] (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

65. Martin Study No. 744
Item II. D. 3. Vol. 1.1, p. 78
Item VII. F. 1. a. i. Vol. 1.31, p. 1228

ADVERSE REACTIONS[66]

PEPCID is usually well tolerated; most adverse reactions have been mild and transient. The adverse reactions listed below have been reported during domestic and international clinical trials in 2089 patients. In those controlled clinical trials in which PEPCID was compared to placebo, the ~~overall~~ incidence of adverse experiences in the group which received PEPCID, 40 mg at bedtime, was similar to that in the placebo group. No antiandrogenic or other adverse hormonal effects have been observed.

66. Safety Summary
Item II. D. 4. Vol. 1.1, p. 131
Item VII. C. 2. Vol. 1.27, p. 218

The following adverse reactions have been reported ~~at a rate of greater~~ to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.2%), dizziness (1.1%), constipation (1.2%) and diarrhea (1.2%).

PEPCID™
(Famotidine, MSD)

ADVERSE REACTIONS (cont'd)

Other reactions have been reported in clinical trials but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: palpitations

Gastrointestinal: nausea, vomiting, abdominal discomfort, anorexia, dry mouth

Hypersensitivity: orbital edema

Musculoskeletal: musculoskeletal pain, arthralgia

Nervous System/Psychiatric: paresthesias; psychic disturbances including depression, anxiety, decreased libido; insomnia, somnolence

Respiratory: bronchospasm

Skin: alopecia, acne, pruritus, rash, dry skin, flushing

Special Senses: tinnitus, taste disorder

PEPCID™
(Famotidine, MSD)

OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects.[67] In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD_{50} of famotidine in male and female rats and mice was greater than 3000 mg/kg.[68]

DOSAGE AND ADMINISTRATION[69]

Duodenal Ulcer

~~Acute Therapy~~ Healing: The recommended adult oral dosage ~~for acute duodenal ulcer~~ is 40 mg once a day at bedtime. Treatment should be given for 4-8 weeks, but the duration of treatment may be shortened if healing can be documented. Healing occurs within 4 weeks in most cases ~~of duodenal ulcer~~.

67. Jensen Study No. 6
Item II. D. 4. Vol. 1.1, p. 127
Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

68. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 34
Item IV. A. 3. b. i. Vol. 1.3, p. 38

69. Dosage and Administration Summary
Item II. D. 4. Vol. 1.1, p. 86
Item VII. B. 2. Vol. 1.27, p. 32

PEPCID™
(Famotidine, MSD)

Maintenance ~~Therapy~~: For the prevention of recurrence ~~of duodenal ulcer, it is recommended that therapy with PEPCID be continued with~~ a dose of 20 mg once a day at bedtime, is recommended.

~~Benign Gastric Ulcer~~

~~Acute Therapy~~ Healing: The recommended adult oral dosage ~~for acute benign gastric ulcer~~ is 40 mg once a day at bedtime. ~~Treatment should be given for~~ 4 to 8 weeks, depending on when ~~but the duration of treatment may be shortened if~~ healing can be documented.

PEPCID™
(Famotidine, MSD)

Gastric Ulcer

In an international double-blind multicenter, study[33] in patients with endoscopically confirmed ~~acute benign~~ gastric ulcers, PEPCID, 40 mg h.s., was compared to placebo h.s. As illustrated in the table below, the ~~rate~~ incidence of ulcer healing with PEPCID was statistically significantly different than placebo, after 4 weeks to 8 weeks of therapy, based on proportion of endoscopically confirmed healed ulcers.

Patients with endoscopically confirmed healed ulcers

	PEPCID 40 mg h.s. (N = 149)	Placebo h.s. (N = 145)
Week 4	*47 %	31 %
Week 6	*65 %	46 %
Week 8	*80 %	54 %

* statistically significantly different than placebo ($p < 0.01$)

In this study, relief of daytime and nighttime pain was quicker for patients on therapy with PEPCID than for patients on placebo; patients on therapy with PEPCID also took antacids significantly less frequently than the patients on placebo, but the difference was not clinically meaningful.

33. International Multicenter Trial vs. Placebo
Item II. D. 4. Vol. 1.1, p. 117
Item VII. F. 2. a. ii. Vol. 1.37, p. 3615

PEPCID™
(Famotidine, MSD)

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome) ~~Multiple Endocrine Adenomas)~~

In studies[34,35] of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome ~~and multiple endocrine adenomas,~~ PEPCID significantly inhibited gastric acid secretion and controlled associated symptoms. Doses from 20 ~~mg p.i.d. to~~ 160 mg q 6h maintained basal acid secretion below 10 mEq/hr.; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. PEPCID was well tolerated at these high dose levels for prolonged periods (greater than 12 months) and there were no cases reported of gynecomastia, increased prolactin levels, or impotence.

34. Jensen Study No. 6
    Item II. O. 4. Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

35. Cohen Study No. 41
    Item II. O. 4. Vol. 1.1, p. 129
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4136

PEPCID™
(Famotidine, MSD)

INDICATIONS AND USAGE

PEPCID is indicated in:

1. Treatment of acute duodenal ulcer.[36,37]

   Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 8 weeks.

2. Prophylactic use in duodenal ulcer disease[38,39]

3. Treatment of acute benign gastric ulcer.[40,41]

   Most patients heal within 8 weeks.

4. Treatment of ~~pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)~~.[42,43]

36. U.S. Multicenter Trial vs. Placebo Acute Phase
    Item II. D. 4. — Vol. 1.1, p. 96
    Item VII. F. 2. a. i. — Vol. 1.35, p. 2922

37. International Multicenter Trial vs. Ranitidine
    Item II. D. 4. — Vol. 1.1, p. 102
    Item VII. F. 2. a. i. — Vol. 1.36, p. 3283

38. U.S. Multicenter Trial vs. Placebo Maintenance Phase
    Item II. D. 4. — Vol. 1.1, p. 108
    Item VII. F. 2. a. i. — Vol. 1.35, p. 2923

39. International Multicenter Trial vs. Placebo
    Item II. D. 4. — Vol. 1.1, p. 113
    Item VII. F. 2. a. i. — Vol. 1.36, p. 3475

40. International Multicenter Trial vs. Placebo
    Item II. D. 4. — Vol. 1.1, p. 117
    Item VII. F. 2. a. ii. — Vol. 1.37, p. 3615

41. Yamanouchi Multicenter Trial vs. Gefarnate
    Item II. D. 4. — Vol. 1.1, p. 123
    Item VII. F. 2. a. ii. — Vol. 1.37, p. 3774

42. Jensen Study No. 6
    Item II. D. 4. — Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. — Vol. 1.38, p. 4028

43. Cohen Study No. 41
    Item II. D. 4. — Vol. 1.1, p. 129
    Item VII. F. 2. a. iii. — Vol. 1.38, p. 4136

PEPCID™
(Famotidine, MSD)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

PRECAUTIONS

General

Symptomatic response to therapy with PEPCID does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency

Dosing intervals may need to be prolonged in patients with severe renal insufficiency (creatinine clearance < 10 mL/min) to adjust for the longer elimination half-life of famotidine.[44] (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). However, no drug-related toxicity has been found with high plasma concentrations of famotidine.[45]

44. Abraham Study No. 404
Item II. D. 3. Vol. 1.1, p. 58
Item V. M. 17. Vol. 1.23, p. 639

45. Jensen Study No. 6
Item II. D. 4. Vol. 1.1, p. 127
Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

PEPCID™
(Famotidine, MSD)

Drug Interactions

No drug interactions have been identified. Studies with famotidine in man, in animal models,[46] and in vitro[47] have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man have included warfarin,[48] theophylline.[49] phenytoin,[50] diazepam,[51] aminopyrine[52] and antipyrine.[52] Indocyanine green as an index of hepatic blood flow and/or hepatic drug extraction has been tested and no significant effects have been found.[50]

46. Preclinical Pharmacology
    Item II D. 2. Vol. 1.1, p. 33
    Item IV. D. 2. (19) Vol. 1.5, p. 1232

47. Preclinical Pharmacology
    Item II D. 2. Vol. 1.1, p. 33
    Item IV D. 2. (20) Vol. 1.5, p. 1257

48. Ryan Study No. 53
    Item II D. 3. Vol. 1.1, p. 84
    Item VII. F. 1. a. iv. Vol. 1.34, p. 2725

49. Williams Study No. 48
    Item II D. 3. Vol. 1.1, p. 82
    Item VII. F. 1. a. iv. Vol. 1.34, p. 2375

50. Williams Study No. 55
    Item II D. 3. Vol. 1.1, p. 83
    Item VII. F. 1. a. iv. Vol. 1.34, p. 2472

51. Zinny Study No. 58
    Item II D. 3. Vol. 1.1, p. 81
    Item VII. F. 1. a. iv. Vol. 1.33, p. 2284

52. Langman Study No. 690
    Item II D. 3. Vol. 1.1, p. 80
    Item VII. F. 1. a. iv. Vol. 1.33, p. 2201

PEPCID™
(Famotidine, MSD)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 106 week study[53] in rats and a 92 week study[54] in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the maximum recommended human dose), there was no evidence of carcinogenic potential for PEPCID.

Famotidine was negative in the microbial mutagen test (Ames test) using Salmonella typhimurium and Escherichia coli with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate.[55] In in vivo studies in mice with a micronucleus test[56] and a chromosomal aberration test[57], no evidence of a mutagenic effect was observed.

In studies with rats given oral doses[58] of up to 2000 mg/kg/day or intravenous doses[59] of up to 200 mg/kg/day (approximately 2500 and 250 times the maximum recommended human dose, respectively), fertility and reproductive performance were not affected.

53. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 41
Item IV. D. 6. (3). Vol. 1.19, p. 6510

54. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 41
Item IV. D. 6. (2). Vol. 1.18, p. 6113

55. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 40
Item IV. D. 5. (1). Vol. 1.17, p. 5817

56. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 40
Item IV. D. 5. (12). Vol. 1.17, p. 5972

57. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 40
Item IV. D. 5. (13). Vol. 1.17, p. 5985

58. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 37
Item IV. D. 4. (11). Vol. 1.15, p. 4997

59. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (12). Vol. 1.16, p. 5266

Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats [60,61] and rabbits [62,63] at oral doses of up to 2000 and 500 mg/kg/day, respectively (approximately 2500 and 625 times the maximum recommended human dose, respectively), and have revealed no evidence of impaired fertility or harm to the fetus due to PEPCID. There are, however, no adequate or well-controlled studies in pregnant women.

Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies performed in lactating rats have shown that famotidine is secreted in breast milk.[64] It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from PEPCID, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

60. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 37
Item IV. D. 4. (1). Vol. 1.12, p. 4106

61. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (2). Vol. 1.13, p. 4144

62. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (5). Vol. 1.14, p. 4671

63. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 38
Item IV. D. 4. (6). Vol. 1.15, p. 4753

64. Preclinical Toxicology
Item II. D. 2. Vol. 1.1, p. 33
Item IV. D. 2. (15). Vol. 1.5, p. 1187

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

No dosage adjustment is required based on age[65] (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

65. Martin Study No. 744
Item II. D. 3. Vol. 1.1, p. 78
Item VII. F. 1. a. i. Vol. 1.31, p. 1228

ADVERSE REACTIONS[66]

PEPCID is usually well tolerated; most adverse reactions have been mild and transient. The adverse reactions listed below have been reported during domestic and international clinical trials in 2089 patients. In those controlled clinical trials in which PEPCID was compared to placebo, the ~~overall~~ incidence of adverse experiences in the group which received PEPCID 40 mg at bedtime was similar to that in the placebo group. No antiandrogenic or other adverse hormonal effects have been observed.

66. Safety Summary
Item II. D. 4. Vol. 1.1, p. 131
Item VII. C. 2. Vol. 1.27, p. 218

The following adverse reactions have been reported ~~at a rate of greater~~ to occur in more than 1% ~~in~~ of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.2%), dizziness (1.1%), constipation (1.2%) and diarrhea (1.2%).

PEPCID™
(Famotidine, MSD)

ADVERSE REACTIONS (cont'd)

Other reactions have been reported in clinical trials but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: palpitations

Gastrointestinal: nausea, vomiting, abdominal discomfort, anorexia, dry mouth

Hypersensitivity: orbital edema

Musculoskeletal: musculoskeletal pain, arthralgia

Nervous System/Psychiatric: paresthesias; psychic disturbances including depression, anxiety, decreased libido; insomnia, somnolence

Respiratory: bronchospasm

Skin: alopecia, acne, pruritus, rash, dry skin, flushing

Special Senses: tinnitus, taste disorder

PEPCID™
(Famotidine, MSD)

OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects.[67] In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD_{50} of famotidine in male and female rats and mice was greater than 3000 mg/kg.[68]

DOSAGE AND ADMINISTRATION[69]

Duodenal Ulcer

~~Acute Therapy~~ Healing: The recommended adult oral dosage ~~for acute duodenal ulcer~~ is 40 mg once a day at bedtime. Treatment should be given for 4-8 weeks, but the duration of treatment may be shortened if healing can be documented. Healing occurs within 4 weeks in most cases ~~of duodenal ulcer~~.

67. Jensen Study No. 6
    Item II. D. 4. Vol. 1.1, p. 127
    Item VII. F. 2. a. iii. Vol. 1.38, p. 4028

68. Preclinical Toxicology
    Item II. D. 2. Vol. 1.1, p. 34
    Item IV. A. 3. b. i. Vol. 1.3, p. 38

69. Dosage and Administration
    Summary
    Item II. D. 4. Vol. 1.1, p. 86
    Item VII. B. 2. Vol. 1.27, p. 32

PEPCID™
(Famotidine, MSD)

Maintenance ~~Therapy~~: For the prevention of recurrence ~~of duodenal ulcer, it is recommended that therapy with PEPCID be continued with~~ a dose of 20 mg once a day at bedtime, is recommended.

~~Benign Gastric Ulcer~~

~~Acute Therapy~~ Healing: The recommended adult oral dosage ~~for acute benign gastric ulcer~~ is 40 mg once a day at bedtime. ~~Treatment should be given~~ for 4 to 8 weeks, depending on when ~~but the duration of treatment may be shortened if~~ healing can be documented.

PEPCID®
(Famotidine, MSD)

~~Pathological Hypersecretory Conditions~~

~~(such as Zollinger-Ellison Syndrome, multiple endocrine adenomas)~~

The dosage of PEPCID ~~in patients with pathological hypersecretory conditions~~ varies with the individual patient. The recommended adult oral starting dose ~~for pathological hypersecretory conditions~~ is 20 mg q6h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q6h have been administered to some patients ~~with severe Zollinger-Ellison syndrome~~.

Concomitant Use ~~with~~ of Antacids[70]

Antacids may be given concomitantly if needed.

70. Kann Study No. 47
Item II. D. 3. Vol. 1.1, p. 76
Item V. M. 24. Vol. 1.25, p. 13

Dosage Adjustment for Patients with Severe Renal Insufficiency

In patients with severe renal insufficiency, i.e., with a creatinine clearance less than 10 mL/min., the elimination half-life of PEPCID may exceed 20 hours, reaching approximately 24 hours in anuric patients.[71] Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosing interval of PEPCID may be prolonged to 36-48 hours as indicated by the patient's clinical response.

71. Abraham Study No. 404
Item II. D. 3. Vol. 1.1, p. 58
Item V. M. 17. Vol. 1.23, p. 6

PEPCID™
(Famotidine, MSD) XXXXXX

HOW SUPPLIED[72]

Tablets PEPCID are "D"-shaped, film-coated tablets supplied as follows:

No. XXXX - 20 mg beige colored, coded MSD 963.

NDC 0006-0963-30 unit of use bottles of 30

NDC 0006-0963-61 unit of use bottles of 60

NDC 0006-0963-28 unit dose package of 100.

No. XXXX - 40 mg light brownish orange, coded MSD 964.

NDC 0006-0964-30 unit of use bottles of 30

NDC 0006-0964-61 unit of use bottles of 60

NDC 0006-0964-28 unit dose package of 100.

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72. Chemistry, Manufacturing and Controls
Item II. D. 1. Vol. 1.1, p. 027
Item III. B. 4 Vol. 1.2, p. 109

NDA
19462

Chem
Rev

DIVISION OF CARDIO-RENAL DRUG PRODUCT
CHEMIST'S REVIEW #3

Date Completed: March 31, 1986

A. 1. NDA 19-462:

Sponsor: Merck Sharp and Dohme

Address: West Point, Penn 19486

AF #: 12-611

2. Product Name (s):

Proprietary- Pepcid

Nonproprietary- Famotidine

USAN- as above

Compendium- none listed

Code Name and/or number-
Refer to Chemist's Revie

3. Dosage Form and Route of Administration:
Oral tablets of 20 and 40 mg deveoped for marketing.

4. Pharmacological Category and/or Prinicpal Indications:

Potent, long-acting H_2 receptor antagonist (healer to peptic ulcers).

5. Structural Formula and Chemical Name:
See Chemist Review #1

B. 1. Initinal Submission: Receipt Date: 06-24-85
Filing Date: 08-22-85

2. Amendments:

D. Conclusions:

This application is now considered to be approvable from the standpoint of manufacturing controls. The SBA has been changed to reflect this under the "Methods Validation" section.

Stuart Zimmerman

Stuart Zimmerman, Ph.D.

4-11-86

cc:
ORIG
HFN-110
HFN-110/CSO
HFN-110/SZimmerman/4/3/86
cb/4/3/86/0871v
R/D init RWolters/4/8/86

USDA
1962

FPL

NDA 19-462

A.H.F.S. Category: 56:40

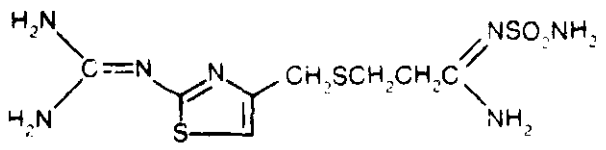
7452200

MSD | PEPCID® TABLETS (FAMOTIDINE, MSD)

PEPCID®
(Famotidine, MSD)

DESCRIPTION

The active ingredient in PEPCID* Tablets (Famotidine, MSD), is a histamine H_2 receptor antagonist. Famotidine is 3-[[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-*N*-(aminosulfonyl) propanimidamide. The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.43. Its structural formula is:



Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl* cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

GI Effects

PEPCID is a competitive inhibitor of histamine H_2-receptors. The primary clinically important pharmacologic activity of PEPCID is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by PEPCID, while changes in pepsin secretion are proportional to volume output.

In normal volunteers and hypersecretors, PEPCID inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. After oral administration, 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.

After intravenous administration, the maximum effect was achieved within 30 minutes. Single intravenous doses of 10 and 20 mg inhibited nocturnal secretion for a period of 10 to 12 hours. The 20 mg dose was associated with the longest duration of action in most subjects.

Single evening oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects; mean nocturnal gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours. The same doses given in the morning suppressed food-stimulated acid secretion in all subjects. The mean suppression was 76% and 84% respectively 3 to 5 hours after administration, and 25% and 30% respectively 8 to 10 hours after administration. In some subjects who received the 20 mg dose, however, the antisecretory effect was dissipated within 6-8 hours. There was no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of PEPCID to mean values of 5.0 and 6.4, respectively. When PEPCID was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of PEPCID was raised to about 5.

PEPCID had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by PEPCID.

Other Effects

Systemic effects of PEPCID in the CNS, cardiovascular, respiratory or endocrine systems have not been found to date. Serum prolactin levels did not rise after intravenous 20 mg bolus doses of PEPCID. No antiandrogenic effects have been detected.

Pharmacokinetics

PEPCID is incompletely absorbed. The bioavailability of oral doses is 40-45%. Bioavailability may be slightly increased by food, or slightly decreased by antacids; however, these effects are of no clinical consequence. PEPCID undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen to 20% of PEPCID in plasma is protein bound. PEPCID has an elimination half-life of 2.5-3.5 hours. PEPCID is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 mL/min, indicating some tubular excretion. Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide.

There is a close relationship between creatinine clearance values and the elimination half-life of PEPCID. In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min, PEPCID elimination half-life may exceed 20 hours and adjustment of dose or dosing intervals may be necessary (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of PEPCID.

Clinical Studies

Duodenal Ulcer

In a U.S. multicenter double-blind study in outpatients with endoscopically confirmed duodenal ulcer, orally administered PEPCID was compared to placebo. As shown in the table below, 70% of patients treated with PEPCID 40 mg h.s. were healed by Week 4.

Outpatients with endoscopically confirmed healed ulcers

	PEPCID 40 mg h.s. (N = 69)	PEPCID 20 mg b.i.d. (N = 34)	Placebo h.s. (N = 97)
Week 2	*32%	*38%	17%
Week 4	*70%	*67%	31%

*Statistically significantly different than placebo ($p \leq 0.001$)

Patients not healed by Week 4 were continued in the study. By Week 8, 83% of patients treated with PEPCID had healed versus 45% of patients treated with placebo. The incidence of ulcer healing with PEPCID was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

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(Famotidine, MSD)

7452200

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients receiving PEPCID than for patients receiving placebo; patients receiving PEPCID also took less antacid than the patients receiving placebo.

Long-Term Maintenance Treatment of Duodenal Ulcers

PEPCID, 20 mg p.o. h.s. was compared to placebo h.s. as maintenance therapy in two double-blind, multicenter studies of patients with endoscopically confirmed healed duodenal ulcers. In the U.S. study the observed ulcer incidence within 12 months in patients treated with placebo was 2.4 times greater than in the patients treated with PEPCID. The 89 patients treated with PEPCID had a cumulative observed ulcer incidence of 23.4% compared to an observed ulcer incidence of 56.6% in the 89 patients receiving placebo ($p < 0.01$). These results were confirmed in an international study where the cumulative observed ulcer incidence within 12 months in the 307 patients treated with PEPCID was 35.7%, compared to an incidence of 75.5% in the 325 patients treated with placebo ($p < 0.01$).

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)

In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome with or without multiple endocrine adenomas, PEPCID significantly inhibited gastric acid secretion and controlled associated symptoms. Doses from 20 to 160 mg q 6 h maintained basal acid secretion below 10 mEq/hr; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. PEPCID was well tolerated at these high dose levels for prolonged periods (greater than 12 months) in eight patients, and there were no cases reported of gynecomastia, increased prolactin levels, or impotence.

INDICATIONS AND USAGE

PEPCID is indicated in:

1. *Short term treatment of active duodenal ulcer.* Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.

2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies have not extended beyond one year.

3. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas).*

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

PRECAUTIONS

General

Symptomatic response to therapy with PEPCID does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency

Longer intervals between doses or lower doses may need to be used in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.) However, currently, no drug-related toxicity has been found with high plasma concentrations of famotidine.

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Drug Interactions

No drug interactions have been identified. Studies with famotidine in man, in animal models, and *in vitro* have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for PEPCID.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate. In *in vivo* studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day, fertility and reproductive performance were not affected.

Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day, respectively, and in both species at I.V. doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to PEPCID. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 600 times the usual human dose. It is not known whether this drug is secreted into human milk. Because many drugs are secreted into human milk and because of the potential for serious adverse reactions in nursing infants from PEPCID, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). Dosage adjustment in the case of severe renal impairment may be necessary.

ADVERSE REACTIONS

The adverse reactions listed below have been reported during domestic and international clinical trials in approx-

PEPCID®
(Famotidine, M

imately 2500 patients. In those c
which PEPCID Tablets were comp
dence of adverse experiences in
PEPCID Tablets, 40 mg at bedtime
placebo group.

The following adverse reaction
occur in more than 1% of patients
controlled clinical trials, and may
drug: headache (4.7%), dizziness
and diarrhea (1.7%).

The following other adverse rea
in clinical trials. While a causal
established for these infrequently
cannot be excluded.

Body as a Whole: fever, asthenia

Cardiovascular: palpitations

Gastrointestinal: nausea, vomiti
anorexia, dry mouth, liver enzyme

Hematologic: thrombocytopenia

Hypersensitivity: orbital edema,

Musculoskeletal: musculoskelet

Nervous System/Psychiatric: pa
zure (single report); psychic distur
sion, anxiety, decreased libido, hall
insomnia; somnolence

Respiratory: bronchospasm

Skin: alopecia, acne, pruritus, ra

Special Senses: tinnitus, taste di

OVERDOSA

There is no experience to date wi
Doses of up to 640 mg/day have b
pathological hypersecretory con
adverse effects. In the event of over
be symptomatic and supportiv
should be removed from the gastro
should be monitored, and suppo
employed.

The oral LD_{50} of famotidine in r
mice was greater than 3000 mg/kg
acute oral dose in dogs exceeded 20
not produce overt effects at high ora
and dogs, but induced significan
depression in rabbits starting with
intravenous LD_{50} of famotidine for
254-563 mg/kg and the minimum
dogs was approximately 300 mg/k
tion in I.V. treated dogs were eme

Issued October 1986

NDA 19-46

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dine, MSD)

e been identified. Studies with models, and *in vitro* have shown th the disposition of compounds ic microsomal enzymes, e.g., mpounds tested in man include nytoin, diazepam, aminopyrine green as an index of hepatic drug and no significant effects have

s, Impairment of Fertility
ts and a 92 week study in mice 2000 mg/kg/day (approximately ed human dose for active duo- idence of carcinogenic potential

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oral doses of up to 2000 mg/kg/ up to 200 mg/kg/day fertility and vere not affected.

been performed in rats and rab- 2000 and 500 mg/kg/day respec- I.V. doses of up to 200 mg/kg/day, cant evidence of impaired fertility PEPCID. While no direct fetotoxic d, sporadic abortions occurring marked decreased food intake oral doses of 200 mg/kg/day (250 e) or higher. There are, however, lled studies in pregnant women. e studies are not always predic- is drug should be used during ded.

ting rats have shown that fam- t milk. Transient growth depres- ig rats suckling from mothers doses of at least 600 times the t known whether this drug is ecause many drugs are secreted se of the potential for serious infants from PEPCID, a decision o discontinue nursing or discon- ccount the importance of the drug

in children have not been estab-

is required based on age (see GY, *Pharmacokinetics*). Dosage severe renal impairment may be

E REACTIONS
sted below have been reported national clinical trials in approx-

PEPCID®
(Famotidine, MSD)

imately 2500 patients. In those controlled clinical trials in which PEPCID Tablets were compared to placebo, the incidence of adverse experiences in the group which received PEPCID Tablets, 40 mg at bedtime, was similar to that in the placebo group.

The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

The following other adverse reactions have been reported in clinical trials. While a causal relationship could not be established for these infrequently reported events, causality cannot be excluded.

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: palpitations

Gastrointestinal: nausea, vomiting, abdominal discomfort, anorexia, dry mouth, liver enzyme abnormalities

Hematologic: thrombocytopenia

Hypersensitivity: orbital edema, conjunctival injection

Musculoskeletal: musculoskeletal pain, arthralgia

Nervous System/Psychiatric: paresthesias; grand mal seizure (single report); psychic disturbances including depression, anxiety, decreased libido, hallucinations (single report); insomnia; somnolence

Respiratory: bronchospasm

Skin: alopecia, acne, pruritus, rash, dry skin, flushing

Special Senses: tinnitus, taste disorder

OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD_{50} of famotidine in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 2000 mg/kg. Famotidine did not produce overt effects at high oral doses in mice, rats, cats and dogs, but induced significant anorexia and growth depression in rabbits starting with 200 mg/kg/day orally. The intravenous LD_{50} of famotidine for mice and rats ranged from 254-563 mg/kg and the minimum lethal single I.V. dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in I.V. treated dogs were emesis, restlessness, pallor of

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(Famotidine, MSD)

mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended oral dose is 20 mg once a day at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome, multiple endocrine adenomas)

The dosage of PEPCID in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q 6 h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q 6 h have been administered to some patients with severe Zollinger-Ellison Syndrome.

Concomitant Use of Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency

In patients with severe renal insufficiency, i.e., with a creatinine clearance less than 10 mL/min, the elimination half-life of PEPCID may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dose of PEPCID may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

HOW SUPPLIED

No. 3535—PEPCID Tablets, 20 mg, are beige colored, U-shaped, film-coated tablets coded MSD 963. They are supplied as follows:

NDC 0006-0963-30 bottles of 30
NDC 0006-0963-28 unit dose package of 100.

No. 3536—PEPCID Tablets, 40 mg, are light brownish-orange, U-shaped, film-coated tablets coded MSD 964. They are supplied as follows:

NDC 0006-0964-30 bottles of 30
NDC 0006-0964-28 unit dose package of 100.

Storage

Avoid storage at temperatures above 40°C (104°F).

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DIV OF MERCK & CO., INC., WEST POINT, PA 19486, USA

Issued October 1986

Printed in USA

A.H.F.S. Category: 56:40

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MSD

TABLETS
PEPCID®
(FAMOTIDINE, MSD)

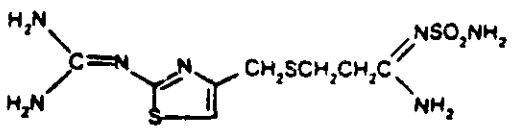
ORAL SUSPENSION
PEPCID®
(FAMOTIDINE FOR ORAL SUSPENSION, MSD)

INJECTION
PEPCID® I.V.
(FAMOTIDINE, MSD)

Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension, MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

DESCRIPTION

The active ingredient in PEPCID* (Famotidine, MSD), is a histamine H_2-receptor antagonist. Famotidine is 3-[[2-[(aminoiminomethyl) amino]-4-thiazolyl]methyl]thio]-*N*-(aminosulfonyl) propanimidamide. The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.43. Its structural formula is:



Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Famotidine is supplied in three dosage forms: PEPCID Tablets, PEPCID Oral Suspension, and PEPCID I.V.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, titanium dioxide.

Each 5 mL of the oral suspension when prepared as directed contains 40 mg of famotidine and the following inactive ingredients: citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose and xanthan gum. Added as preservatives are sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02%.

Each mL of the solution for intravenous injection contains 10 mg of famotidine and the following inactive ingredients: L-aspartic acid 4 mg, mannitol 20 mg, and Water for Injection q.s. 1 mL. The multidose injection also contains benzyl alcohol 0.9% added as preservative.

CLINICAL PHARMACOLOGY

GI Effects

PEPCID is a competitive inhibitor of histamine H_2-receptors. The primary clinically important pharmacologic activity of PEPCID is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by PEPCID, while changes in pepsin secretion are proportional to volume output.

In normal volunteers and hypersecretors, PEPCID inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. After oral administration, 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.

After intravenous administration, the maximum effect was achieved within 30 minutes. Single intravenous doses of 10 and 20 mg inhibited nocturnal secretion for a period of 10 to 12 hours. The 20 mg dose was associated with the longest duration of action in most subjects.

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Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension, MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

Single evening oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects; mean nocturnal gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours. The same doses given in the morning suppressed food-stimulated acid secretion in all subjects. The mean suppression was 76% and 84% respectively 3 to 5 hours after administration, and 25% and 30% respectively 8 to 10 hours after administration. In some subjects who received the 20 mg dose, however, the antisecretory effect was dissipated within 6-8 hours. There was no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of PEPCID to mean values of 5.0 and 6.4, respectively. When PEPCID was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of PEPCID was raised to about 5.

PEPCID had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by PEPCID.

Other Effects

Systemic effects of PEPCID in the CNS, cardiovascular, respiratory or endocrine systems have not been found to date. Serum prolactin levels did not rise after intravenous 20 mg bolus doses of PEPCID. No antiandrogenic effects have been detected.

Pharmacokinetics

PEPCID is incompletely absorbed. The bioavailability of oral doses is 40-45%. PEPCID Tablets and PEPCID Oral Suspension are bioequivalent. Bioavailability may be slightly increased by food, or slightly decreased by antacids; however, these effects are of no clinical consequence. PEPCID undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen to 20% of PEPCID in plasma is protein bound. PEPCID has an elimination half-life of 2.5-3 hours. PEPCID is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 mL/min, indicating some tubular excretion. Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide.

There is a close relationship between creatinine clearance values and the elimination half-life of PEPCID. In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min, PEPCID elimination half-life may exceed 20 hours and adjustment of dose or dosing intervals may be necessary (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of PEPCID.

Clinical Studies

Duodenal Ulcer

In a U.S. multicenter, double-blind study in outpatients with endoscopically confirmed duodenal ulcer, orally administered PEPCID was compared to placebo. As shown in the table below, 70% of patients treated with PEPCID 40 mg h.s. were healed by week 4.

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Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension, MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

Outpatients with endoscopically confirmed healed ulcers

	PEPCID 40 mg h.s. (N = 88)	PEPCID 20 mg b.i.d. (N = 84)	Placebo h.s. (N = 97)
Week 2	*32%	*38%	17%
Week 4	*70%	*67%	31%

*Statistically significantly different than placebo ($p < 0.001$)

Patients not healed by week 4 were continued in the study. By week 8, 83% of patients treated with PEPCID had healed versus 45% of patients treated with placebo. The incidence of ulcer healing with PEPCID was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients receiving PEPCID than for patients receiving placebo; patients receiving PEPCID also took less antacid than the patients receiving placebo.

Long-Term Maintenance
Treatment of Duodenal Ulcers

PEPCID, 20 mg p.o. h.s. was compared to placebo h.s. as maintenance therapy in two double-blind, multicenter studies of patients with endoscopically confirmed healed duodenal ulcers. In the U.S. study the observed ulcer incidence within 12 months in patients treated with placebo was 2.4 times greater than in the patients treated with PEPCID. The 89 patients treated with PEPCID had a cumulative observed ulcer incidence of 23.4% compared to an observed ulcer incidence of 56.6% in the 89 patients receiving placebo ($p<0.01$). These results were confirmed in an international study where the cumulative observed ulcer incidence within 12 months in the 307 patients treated with PEPCID was 36.7%, compared to an incidence of 75.5% in the 325 patients treated with placebo ($p<0.01$).

Gastric Ulcer

In both a U.S. and an international multicenter, double-blind study in patients with endoscopically confirmed active benign gastric ulcer, orally administered PEPCID, 40 mg h.s., was compared to placebo h.s. Antacids were permitted during the studies, but consumption was not significantly different between the PEPCID and placebo groups. As shown in the table below, the incidence of ulcer healing (dropouts counted as unhealed) with PEPCID was statistically significantly better than placebo at weeks 6 and 8 in the U.S. study, and at weeks 4, 6 and 8 in the international study, based on the number of ulcers that healed, confirmed by endoscopy.

Patients with endoscopically confirmed healed ulcers

	U.S. Study		International Study	
	PEPCID 40 mg h.s. (N = 74)	Placebo h.s. (N = 75)	PEPCID 40 mg h.s. (N = 149)	Placebo h.s. (N = 145)
Week 4	45%	39%	**47%	31%
Week 6	**68%	44%	**65%	46%
Week 8	*78%	64%	**80%	54%

*,**Statistically significantly better than placebo ($p \leq 0.05$, $p \leq 0.01$ respectively)

Time to complete relief of daytime and nighttime pain was statistically significantly shorter for patients receiving PEPCID than for patients receiving placebo; however, in neither study was there a statistically significant difference in the proportion of patients whose pain was relieved by the end of the study (week 8).

Pathological Hypersecretory Conditions
(e.g., Zollinger-Ellison Syndrome,
Multiple Endocrine Adenomas)

In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome with or without multiple endocrine adenomas, PEPCID significantly inhibited gastric acid secretion and controlled associated symptoms. Doses from 20 to 160 mg q 6 h maintained basal acid secretion below 10 mEq/hr; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. PEPCID was well tolerated at these high dose levels for prolonged periods (greater than 12 months) in eight patients, and there were no cases reported of gynecomastia, increased prolactin levels, or impotence.

Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension, MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

INDICATIONS AND USAGE

PEPCID is indicated in:

1. *Short term treatment of active duodenal ulcer.* Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.
2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies have not extended beyond one year.
3. *Short term treatment of active benign gastric ulcer.* Most patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.
4. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas).*

PEPCID I.V. is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or as an alternative to the oral dosage forms for short-term use in patients who are unable to take oral medication.

CONTRAINDICATIONS

Hypersensitivity to any component of these products.

PRECAUTIONS

General

Symptomatic response to therapy with PEPCID does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency

Longer intervals between doses or lower doses may need to be used in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.) However, currently, no drug-related toxicity has been found with high plasma concentrations of famotidine.

Information for Patients

The patient should be instructed to shake the oral suspension vigorously for 5 - 10 seconds prior to each use. Unused constituted oral suspension should be discarded after 30 days.

Drug Interactions

No drug interactions have been identified. Studies with famotidine in man, in animal models, and *in vitro* have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

Carcinogenesis, Mutagenesis,
Impairment of Fertility

In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for PEPCID.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate. In *in vivo* studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day fertility and reproductive performance were not affected.

Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day respectively and in both species at I.V. doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to PEPCID. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 500 times the usual human dose. It is not known whether this drug is secreted into human milk. Because many drugs are secreted into human milk and because of the potential for serious adverse reactions in nursing infants from PEPCID, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). Dosage adjustment in the case of severe renal impairment may be necessary.

ADVERSE REACTIONS

The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In those controlled clinical trials in which PEPCID Tablets were compared to placebo, the incidence of adverse experiences in the group which received PEPCID Tablets, 40 mg at bedtime, was similar to that in the placebo group.

The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

The following other adverse reactions have been reported in clinical trials. While a causal relationship could not be established for these infrequently reported events, causality cannot be excluded.

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: palpitations

Gastrointestinal: nausea, vomiting, abdominal discomfort, anorexia, dry mouth, liver enzyme abnormalities

Hematologic: thrombocytopenia

Hypersensitivity: orbital edema, conjunctival injection

Musculoskeletal: musculoskeletal pain, arthralgia

Nervous System/Psychiatric: paresthesia; grand mal seizure (single report); psychic disturbances including depression, anxiety, decreased libido, hallucinations (single report); insomnia; somnolence

Respiratory: bronchospasm

Skin: alopecia, acne, pruritus, dry skin, flushing

Special Senses: tinnitus, taste disorder

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V. In addition, transient irritation at the injection site has been observed with PEPCID I.V.

OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD_{50} of famotidine in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 2000 mg/kg. Famotidine did not produce overt effects at high oral doses in mice, rats, cats and dogs, but induced significant anorexia and growth depression in rabbits starting with 200 mg/kg/day orally. The intravenous LD_{50} of famotidine for mice and rats ranged from 254-563 mg/kg and the minimum lethal single I.V. dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in I.V. treated dogs were emesis, restlessness, pallor of mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended oral dose is 20 mg once a day at bedtime.

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Benign Gastric Ulcer

Acute Therapy: The recommended adult oral dosage for active benign gastric ulcer is 40 mg once a day at bedtime.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)

The dosage of PEPCID in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q 6 h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q 6 h have been administered to some patients with severe Zollinger-Ellison Syndrome.

Oral Suspension

PEPCID Oral Suspension may be substituted for PEPCID Tablets in any of the above indications for those patients who cannot swallow tablets. Each five mL contains 40 mg of famotidine after constitution of the powder with 46 mL of Purified Water as directed.

Directions for Preparing PEPCID Oral Suspension

Prepare suspension at time of dispensing. Slowly add 46 mL of Purified Water. Shake vigorously for 5 - 10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension

Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration

In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, PEPCID I.V. may be administered. The recommended dosage is 20 mg q 12 h.

Preparation of PEPCID Intravenous Solutions

Dilute 2 mL of PEPCID I.V. (solution containing 10 mg/mL) with 0.9% Sodium Chloride Injection or other compatible intravenous solution to a total volume of either 5 mL or 10 mL and inject over a period of not less than 2 minutes.

Preparation of PEPCID Intravenous Infusion Solutions

PEPCID I.V. may also be administered as an infusion, 2 mL diluted with 100 mL of 5% dextrose or other compatible solution, and infused over a 15-30 minute period.

Stability of PEPCID I.V.

PEPCID I.V. is stable for 48 hours at room temperature when added to or diluted with most commonly used intravenous solutions, e.g., Water for Injection, 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, Lactated Ringer's Injection, or Sodium Bicarbonate Injection, 5%.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency

In patients with severe renal insufficiency, i.e., with a creatinine clearance less than 10 mL/min, the elimination half-life of PEPCID may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dose of PEPCID may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

HOW SUPPLIED

No. 3535 — Tablets PEPCID, 20 mg, are beige colored, U-shaped, film-coated tablets coded MSD 963. They are supplied as follows:

NDC 0006-0963-31 unit of use bottles of 30
NDC 0006-0963-28 unit dose package of 100.

No. 3536 — Tablets PEPCID, 40 mg, are light brownish-orange, U-shaped, film-coated tablets coded MSD 964. They are supplied as follows:

[redacted]

[redacted] PEPCID® (Famotidine, MSD)
[redacted] Suspension PEPCID®
[redacted] for Oral Suspension, MSD)
[redacted] PEPCID® I.V. (Famotidine, MSD)

[redacted] unit of use bottles of 30
[redacted] 40 mg 30's)
NDC 0006-0864-28 unit dose package of 100.

No. 3838 — Oral Suspension PEPCID is a white to off-white powder containing 400 mg of famotidine for constitution. When constituted as directed, PEPCID Oral Suspension is a smooth, mobile, off-white, homogenous suspension with a cherry-banana-mint flavor, containing 40 mg of famotidine per 5 mL.

NDC 0006-3838-82, bottles containing 400 mg famotidine.

FOR INTRAVENOUS USE ONLY

No. 3839 — Injection PEPCID I.V. 10 mg per 1 mL, is a non-preserved, clear, colorless solution and is supplied as follows:

NDC 0006-3839-04, 10 x 2 mL single dose vials.

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No. 3841—Injection PEPCID I.V. 10 mg per 1 mL, is a clear, colorless solution and is supplied as follows:

NDC 0006-3841-14, 4 mL vials.

Storage

Avoid storage of PEPCID Tablets at temperatures above 40°C (104°F).

Avoid storage of the powder for oral suspension at temperatures above 40°C (104°F). After constitution store the suspension below 30°C (86°F). Do not freeze. Discard unused suspension after 30 days.

Store PEPCID I.V. at 2-8°C (35.6-46.4°F). If solution freezes, bring to room temperature; allow sufficient time to solubilize all the components.

When diluted as recommended (see DOSAGE AND ADMINISTRATION) PEPCID I.V. is stable for 48 hours at room temperature.

MSD MERCK SHARP & DOHME
DIV. OF MERCK & CO., INC., WEST POINT, PA 19486, USA

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MSD

TABLETS
PEPCID®
(FAMOTIDINE, MSD)

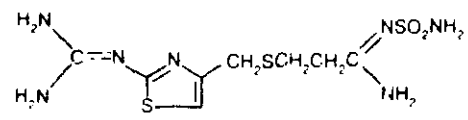
ORAL SUSPENSION
PEPCID®
(FAMOTIDINE FOR ORAL SUSPENSION, MSD)

INJECTION
PEPCID® I.V.
(FAMOTIDINE, MSD)

Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension, MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

DESCRIPTION

The active ingredient in PEPCID® (Famotidine, MSD), is a histamine H_2-receptor antagonist. Famotidine is *N'* -(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide. The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.43. Its structural formula is:



Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Famotidine is supplied in three dosage forms: PEPCID Tablets, PEPCID Oral Suspension, and PEPCID I.V.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, titanium dioxide.

Each 5 mL of the oral suspension when prepared as directed contains 40 mg of famotidine and the following inactive ingredients: citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose and xanthan gum. Added as preservatives are sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02%.

Each mL of the solution for intravenous injection contains 10 mg of famotidine and the following inactive ingredients: L-aspartic acid 4 mg, mannitol 20 mg, and Water for Injection q.s. 1 mL. The multidose injection also contains benzyl alcohol 0.9% added as preservative.

CLINICAL PHARMACOLOGY

GI Effects

PEPCID is a competitive inhibitor of histamine H_2-receptors. The primary clinically important pharmacologic activity of PEPCID is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by PEPCID, while changes in pepsin secretion are proportional to volume output.

In normal volunteers and hypersecretors, PEPCID inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. After oral administration, 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.

After intravenous administration, the maximum effect was achieved within 30 minutes. Single intravenous doses of 10 and 20 mg inhibited nocturnal secretion for a period of 10 to 12 hours. The 20 mg dose was associated with the longest duration of action in most subjects.

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Single evening oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects; mean nocturnal gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours. The same doses given in the morning suppressed food-stimulated acid secretion in all subjects. The mean suppression was 76% and 84% respectively 3 to 5 hours after administration, and 25% and 30% respectively 8 to 10 hours after administration. In some subjects who received the 20 mg dose, however, the antisecretory effect was dissipated within 6-8 hours. There was no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of PEPCID to mean values of 5.0 and 6.4, respectively. When PEPCID was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of PEPCID was raised to about 5.

PEPCID had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by PEPCID.

Other Effects

Systemic effects of PEPCID in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no antiandrogenic effects were noted. (See ADVERSE REACTIONS.) Serum hormone levels, including prolactin, cortisol, thyroxine (T_4), and testosterone, were not altered after treatment with PEPCID.

Pharmacokinetics

PEPCID is incompletely absorbed. The bioavailability of oral doses is 40-45%. PEPCID Tablets and PEPCID Oral Suspension are bioequivalent. Bioavailability may be slightly increased by food, or slightly decreased by antacids; however, these effects are of no clinical consequence. PEPCID undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen to 20% of PEPCID in plasma is protein bound. PEPCID has an elimination half-life of 2.5-3.5 hours. PEPCID is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 mL/min, indicating some tubular excretion. Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide.

There is a close relationship between creatinine clearance values and the elimination half-life of PEPCID. In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min, PEPCID elimination half-life may exceed 20 hours and adjustment of dose or dosing intervals may be necessary (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of PEPCID.

Clinical Studies

Duodenal Ulcer

In a U.S. multicenter, double-blind study in outpatients with endoscopically confirmed duodenal ulcer, orally administered PEPCID was compared to placebo. As shown in Table 1, 70% of patients treated with PEPCID 40 mg h.s. were healed by week 4.

Table 1
Outpatients with Endoscopically Confirmed Healed Duodenal Ulcers

	PEPCID 40 mg h.s. (N = 89)	PEPCID 20 mg b.i.d (N = 84)	Placebo h.s. (N = 97)
Week 2	*32%	*38%	17%
Week 4	*70%	*67%	31%

*Statistically significantly different than placebo ($p < 0.001$)

Patients not healed by week 4 were continued in the study. By week 8, 83% of patients treated with PEPCID had healed versus 45% of patients treated with placebo. The incidence of ulcer healing with PEPCID was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients receiving PEPCID than for patients receiving placebo; patients receiving PEPCID also took less antacid than the patients receiving placebo.

Long-Term Maintenance
Treatment of Duodenal Ulcers

PEPCID, 20 mg p.o. h.s. was compared to placebo h.s. as maintenance therapy in two double-blind, multicenter studies of patients with endoscopically confirmed healed duodenal ulcers. In the U.S. study the observed ulcer incidence within 12 months in patients treated with placebo was 2.4 times greater than in the patients treated with PEPCID. The 89 patients treated with PEPCID had a cumulative observed ulcer incidence of 23.4% compared to an observed ulcer incidence of 56.6% in the 89 patients receiving placebo ($p<0.01$). These results were confirmed in an international study where the cumulative observed ulcer incidence within 12 months in the 307 patients treated with PEPCID was 35.7%, compared to an incidence of 75.5% in the 325 patients treated with placebo ($p<0.01$).

Gastric Ulcer

In both a U.S. and an international multicenter, double-blind study in patients with endoscopically confirmed active benign gastric ulcer, orally administered PEPCID, 40 mg h.s., was compared to placebo h.s. Antacids were permitted during the studies, but consumption was not significantly different between the PEPCID and placebo groups. As shown in Table 2, the incidence of ulcer healing (dropouts counted as unhealed) with PEPCID was statistically significantly better than placebo at weeks 6 and 8 in the U.S. study, and at weeks 4, 6 and 8 in the international study, based on the number of ulcers that healed, confirmed by endoscopy.

Table 2
Patients with Endoscopically Confirmed Healed Gastric Ulcers

	U.S. Study		International Study	
	PEPCID 40 mg h.s. (N = 74)	Placebo h.s. (N = 75)	PEPCID 40 mg h.s. (N = 149)	Placebo h.s. (N = 145)
Week 4	45%	39%	**47%	31%
Week 6	**66%	44%	**65%	46%
Week 8	*78%	64%	**80%	54%

*, **Statistically significantly better than placebo ($p \leq 0.05$, $p < 0.01$ respectively)

Time to complete relief of daytime and nighttime pain was statistically significantly shorter for patients receiving PEPCID than for patients receiving placebo; however, in neither study was there a statistically significant difference in the proportion of patients whose pain was relieved by the end of the study (week 8).

Gastroesophageal Reflux Disease (GERD)

PEPCID was compared to placebo in a U.S. study that enrolled patients with symptoms of GERD and without endoscopic evidence of erosion or ulceration of the esophagus. PEPCID 20 mg b.i.d. was statistically significantly superior to 40 mg h.s. and to placebo in providing a successful symptomatic outcome, defined as moderate or excellent improvement of symptoms (Table 3).

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Table 3
% Successful Symptomatic Outcome

	PEPCID 20 mg b.i.d (N = 154)	PEPCID 40 mg h.s (N = 149)	Placebo (N = 73)
Week 6	82**	69	62

**$p < 0.01$ vs Placebo

By two weeks of treatment, symptomatic success was observed in a greater percentage of patients taking PEPCID 20 mg b.i.d. compared to placebo ($p < 0.01$).

Symptomatic improvement and healing of endoscopically verified erosion and ulceration were studied in two additional trials. Healing was defined as complete resolution of all erosions or ulcerations visible with endoscopy. The U.S. study comparing PEPCID 40 mg b.i.d. to placebo and PEPCID 20 mg b.i.d., showed a significantly greater percentage of healing for PEPCID 40 mg b.i.d. at weeks 6 and 12 (Table 4).

Table 4
% Endoscopic Healing - U.S. Study

	PEPCID 40 mg b.i.d. (N = 127)	PEPCID 20 mg b.i.d. (N = 125)	Placebo (N = 66)
Week 6	48**, ++	32	18
Week 12	69**, +	54**	29

**$p \leq 0.01$ vs Placebo
+$p \leq 0.05$ vs PEPCID 20 mg b.i.d
++$p \leq 0.01$ vs PEPCID 20 mg b.i.d

As compared to placebo, patients who received PEPCID had faster relief of daytime and nighttime heartburn and a greater percentage of patients experienced complete relief of nighttime heartburn. These differences were statistically significant.

In the international study, when PEPCID 40 mg b.i.d., was compared to ranitidine 150 mg b.i.d., a statistically significantly greater percentage of healing was observed with PEPCID 40 mg b.i.d. at week 12 (Table 5). There was, however, no significant difference among treatments in symptom relief.

Table 5
% Endoscopic Healing - International Study

	PEPCID 40 mg b.i.d. (N = 175)	PEPCID 20 mg b.i.d. (N = 93)	Ranitidine 150 mg b.i.d. (N = 172)
Week 6	48	52	42
Week 12	71*	68	60

*$p \leq 0.05$ vs Ranitidine 150 mg b.i.d.

Pathological Hypersecretory Conditions
(e.g., Zollinger-Ellison Syndrome,
Multiple Endocrine Adenomas)

In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome with or without multiple endocrine adenomas, PEPCID significantly inhibited gastric acid secretion and controlled associated symptoms. Doses from 20 to 160 mg q 6 h maintained basal acid secretion below 10 mEq/hr; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. PEPCID was well tolerated at these high dose levels for prolonged periods (greater than 12 months) in eight patients, and there were no cases reported of gynecomastia, increased prolactin levels, or impotence which were considered to be due to the drug.

INDICATIONS AND USAGE

PEPCID is indicated in:

1. *Short term treatment of active duodenal ulcer.* Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.

2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies have not extended beyond one year.

3. *Short term treatment of active benign gastric ulcer.* Most patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

4. *Short term treatment of gastroesophageal reflux disease (GERD)*
PEPCID is indicated for short term treatment of patients with symptoms of GERD (see CLINICAL PHARMACOLOGY, *Clinical Studies*)

PEPCID is also indicated for the short term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy (see CLINICAL PHARMACOLOGY, *Clinical Studies*)

5. *Treatment of pathological hypersecretory conditions (e.g., Zollinger Ellison Syndrome, multiple endocrine adenomas).*

PEPCID I.V. is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or as an alternative to the oral dosage forms for short-term use in patients who are unable to take oral medication.

CONTRAINDICATIONS

Hypersensitivity to any component of these products.

PRECAUTIONS

General

Symptomatic response to therapy with PEPCID does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency

Longer intervals between doses or lower doses may need to be used in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.) However, currently, no drug-related toxicity has been found with high plasma concentrations of famotidine.

Information for Patients

The patient should be instructed to shake the oral suspension vigorously for 5 - 10 seconds prior to each use. Unused constituted oral suspension should be discarded after 30 days.

Drug Interactions

No drug interactions have been identified. Studies with famotidine in man, in animal models, and *in vitro* have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, theophylline and antipyrine, indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for PEPCID.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate. In *in vivo* studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day fertility and reproductive performance were not affected.

Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day respectively and in both species at I.V. doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to PEPCID. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 600 times the usual human dose. It is not known whether this drug is secreted into human milk. Because many drugs are secreted into human milk and because of the potential for serious adverse reactions in nursing infants from PEPCID, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension, MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). Dosage adjustment in the case of severe renal impairment may be necessary.

ADVERSE REACTIONS

The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In those controlled clinical trials in which PEPCID Tablets were compared to placebo, the incidence of adverse experiences in the group which received PEPCID Tablets, 40 mg at bedtime, was similar to that in the placebo group.

The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

The following other adverse reactions have been reported infrequently in clinical trials or since the drug was marketed. The relationship to therapy with PEPCID has been unclear in many cases. Within each category the adverse reactions are listed in order of decreasing severity:

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: arrhythmia, AV block, palpitation

Gastrointestinal: cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth

Hematologic: rare cases of agranulocytosis, pancytopenia, leukopenia, thrombocytopenia

Hypersensitivity: anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection

Musculoskeletal: musculoskeletal pain, arthralgia

Nervous System/Psychiatric: grand mal seizure; psychic disturbances, which were reversible in cases for which follow-up was obtained, including hallucinations, confusion, agitation, depression, anxiety, decreased libido, paresthesia; insomnia; somnolence

Respiratory: bronchospasm

Skin: alopecia, acne, pruritus, dry skin, flushing

Special Senses: tinnitus, taste disorder

Other: rare cases of impotence have been reported; however, in controlled clinical trials, the incidence was not greater than that seen with placebo.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V. In addition, transient irritation at the injection site has been observed with PEPCID I.V.

OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD_{50} of famotidine in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 2000 mg/kg. Famotidine did not produce overt effects at high oral doses in mice, rats, cats and dogs, but induced significant anorexia and growth depression in rabbits starting with 200 mg/kg/day orally. The intravenous LD_{50} of famotidine for mice and rats ranged from 254-563 mg/kg and the minimum lethal single I.V. dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in I.V. treated dogs were emesis, restlessness, pallor of mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended oral dose is 20 mg once a day at bedtime.

Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension, MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

Benign Gastric Ulcer

Acute Therapy: The recommended adult oral dosage for active benign gastric ulcer is 40 mg once a day at bedtime.

Gastroesophageal Reflux Disease (GERD)

The recommended oral dosage for treatment of patients with symptoms of GERD is 20 mg b.i.d. for up to 6 weeks. The recommended oral dosage for the treatment of patients with esophagitis including erosions and ulcerations and accompanying symptoms due to GERD is 20 or 40 mg b.i.d. for up to 12 weeks (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Pathological Hypersecretory Conditions
(e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)

The dosage of PEPCID in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q 6 h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q 6 h have been administered to some patients with severe Zollinger-Ellison Syndrome.

Oral Suspension

PEPCID Oral Suspension may be substituted for PEPCID Tablets in any of the above indications. Each five mL contains 40 mg of famotidine after constitution of the powder with 46 mL of Purified Water as directed.

Directions for Preparing PEPCID Oral Suspension

Prepare suspension at time of dispensing. Slowly add 46 mL of Purified Water. Shake vigorously for 5 - 10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension

Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration

In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, PEPCID I.V. may be administered. The recommended dosage is 20 mg q 12 h.

The doses and regimen for parenteral administration in patients with GERD have not been established.

Preparation of PEPCID Intravenous Solutions

Dilute 2 mL of PEPCID I.V. (solution containing 10 mg/mL) with 0.9% Sodium Chloride Injection or other compatible intravenous solution to a total volume of either 5 mL or 10 mL and inject over a period of not less than 2 minutes.

Preparation of PEPCID Intravenous Infusion Solutions

PEPCID I.V. may also be administered as an infusion, 2 mL diluted with 100 mL of 5% dextrose or other compatible solution, and infused over a 15-30 minute period.

Stability of PEPCID I.V.

PEPCID I.V. is stable for 48 hours at room temperature when added to or diluted with most commonly used intravenous solutions, e.g., Water for Injection, 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, Lactated Ringer's Injection, or Sodium Bicarbonate Injection, 5%.

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Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency

In patients with severe renal insufficiency, i.e., with a creatinine clearance less than 10 mL/min, the elimination half-life of PEPCID may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dose of PEPCID may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

HOW SUPPLIED

No. 3535 — Tablets PEPCID, 20 mg, are beige colored, U-shaped, film-coated tablets coded MSD 963. They are supplied as follows:
NDC 0006-0963-31 unit of use bottles of 30
(6505-01-260-0902, 20 mg 30's)
NDC 0006-0963-58 unit of use bottles of 100
NDC 0006-0963-28 unit dose package of 100

No. 3536 — Tablets PEPCID, 40 mg, are light brownish-orange, U-shaped, film-coated tablets coded MSD 964. They are supplied as follows:
NDC 0006-0964-31 unit of use bottles of 30
(6505-01-257-3164, 40 mg 30's)
NDC 0006-0964-58 unit of use bottles of 100
NDC 0006-0964-28 unit dose package of 100
(6505-01-318-0464, 40 mg individually sealed 100's).

No. 3538 — Oral Suspension PEPCID is a white to off-white powder containing 400 mg of famotidine for constitution. When constituted as directed, PEPCID Oral Suspension is a smooth, mobile, off-white, homogeneous suspension with a cherry-banana-mint flavor, containing 40 mg of famotidine per 5 mL.
NDC 0006-3538-92, bottles containing 400 mg famotidine.

FOR INTRAVENOUS USE ONLY

No. 3539 — Injection PEPCID I.V. 10 mg per 1 mL, is a non-preserved, clear, colorless solution and is supplied as follows:
NDC 0006-3539-04, 10 x 2 mL single dose vials
(6505-01-281-1249, 10 mg per mL, 2 mL 10's).

No. 3541—Injection PEPCID I.V. 10 mg per 1 mL, is a clear, colorless solution and is supplied as follows:
NDC 0006-3541-14, 4 mL vials
(6505-01-282-1180, 10 mg per mL, 4 mL)

Storage

Avoid storage of PEPCID Tablets at temperatures above 40°C (104°F).

Avoid storage of the powder for oral suspension at temperatures above 40°C (104°F). After constitution store the suspension below 30°C (86°F). Do not freeze. Discard unused suspension after 30 days.

Store PEPCID I.V. at 2-8°C (36-46°F). If solution freezes, bring to room temperature; allow sufficient time to solubilize all the components.

When diluted as recommended (see DOSAGE AND ADMINISTRATION) PEPCID I.V. is stable for 48 hours at room temperature.

MSD MERCK SHARP & DOHME
DIV. OF MERCK & CO., INC., WEST POINT, PA. 19486, USA

Issued December 1991

Printed in USA

PEPCID®
(Famotidine, MSD)

~~Pathological Hypersecretory Conditions~~

~~(such as Zollinger-Ellison Syndrome, multiple adenomas)~~

The dosage of PEPCID ~~in patients with pathological hypersecretory conditions~~ varies with the individual patient. The recommended adult oral starting dose ~~for pathological hypersecretory conditions~~ is 20 mg q6h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q6h have been administered to some patients, ~~with severe Zollinger-Ellison syndrome~~.

Concomitant Use ~~with~~ of Antacids[70]

Antacids may be given concomitantly if needed.

70. Kann Study No. 47
Item II. D. 3. Vol. 1.1, p. 76
Item V. M. 24. Vol. 1.25, p. 13

Dosage Adjustment for Patients with Severe Renal Insufficiency

In patients with severe renal insufficiency, i.e., with a creatinine clearance less than 10 mL/min., the elimination half-life of PEPCID may exceed 20 hours, reaching approximately 24 hours in anuric patients.[71] Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosing interval of PEPCID may be prolonged to 36-48 hours as indicated by the patient's clinical response.

71. Abraham Study No. 404
Item II. D. 3. Vol. 1.1, p. 58
Item V. M. 17. Vol. 1.23, p. 6

HOW SUPPLIED[72]

Tablets PEPCID are "D"-shaped, film-coated tablets supplied as follows:

No. XXXX - 20 mg beige colored, coded MSD 963.

NDC 0006-0963-30 unit of use bottles of 30

NDC 0006-0963-61 unit of use bottles of 60

NDC 0006-0963-28 unit dose package of 100.

No. XXXX - 40 mg light brownish orange, coded MSD 964.

NDC 0006-0964-30 unit of use bottles of 30

NDC 0006-0964-61 unit of use bottles of 60

NDC 0006-0964-28 unit dose package of 100.

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72. Chemistry, Manufacturing and Controls
Item II. D. 1. Vol. 1.1, p. 027
Item III. B. 4 Vol. 1.2, p. 109

MSD MERCK SHARP & DOHME
DIV OF MERCK & CO., INC.
WEST POINT, PA. 19486, USA

Issued Printed in USA

NDA
19462

Pharm
Rev

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

NDA 19-462 Pepcid (famotidine) August 26, 1985
Merck Sharpe & Dohme

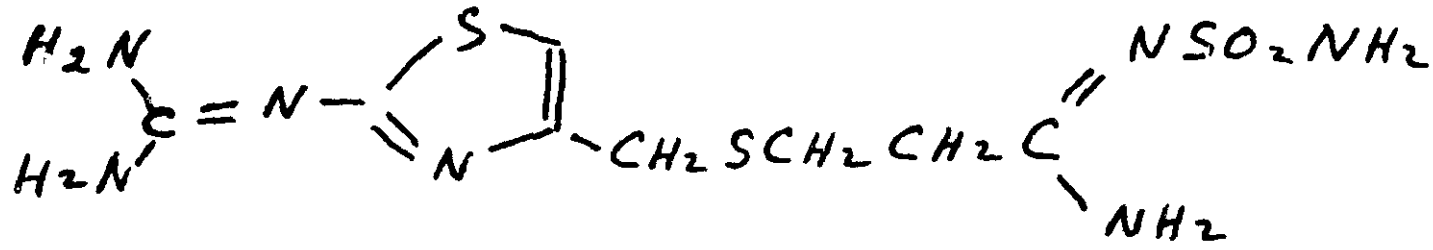
ORIGINAL SUBMISSION CD&B RECEIPT DATE: 6/24/85

Pharmacology Review
(Original Summary)

1. Name of Drug: Pepcid (famotidine) or MK-208

2. Category: Histamine H2 receptor antagonist

3. Chemical Structure:



Famotidine

4. Composition and Dosage Form:

	mg/per tablet
Famotidine.....	20 or 40
plus inactive ingredients	

5. Indications: Short-term treatment of active duodenal and gastric ulcers, long-term prevention of duodenal ulcer recurrence, and long-term management of pathological hypersecretory conditions such as Z-E Syndrome.

6. Dosage: Recommended adult dose is 40mg at bedtime for acute duodenal or gastric ulcer. The maintenance dose to prevent ulcer recurrence is 20mg at bedtime. For Z-E the dose is usually 20mg q.i.d. but could range up to 160mg q.i.d. In patients with renal insufficiency, dosing may be every other day for whatever indication.

7. IND UNDER WHICH CLINICAL STUDIES CONDUCTED: [redacted]

8. Submitted Preclinical Data: These studies were largely conducted either by Yamanouchi Pharm. of Japan (Y) or Merck Sharpe & Dohme (MSD). Many of these studies were reviewed in the past in conjunction with IND 18,888. The following summarizes preclinical data that have not been previously reviewed. For the sake of brevity, the letters F, C, and R are used for Famotidine, Cimetidine, and Ranitidine respectively.

A) Acute Toxicity:

Dogs:

Four dogs treated at separate times with single oral doses ranging from 10 to 2000mg/kg showed no adverse effects (clinical, ECG, serum biochem, body weight, hematology, urinalysis). When the same dogs were subsequently tested for 15 consecutive days with 1000mg/kg/day, they exhibited only slight weight loss and necropsy was normal.

Another set of dogs were tested acutely i.v. with a 2 or 3% formulation containing saline and L-Aspartic acid at doses ranging from 10 to 300 mg/kg injected at the rate of 10 ml/minute. No deaths occurred up to 200 mg/kg but one died at 300 mg/kg of unknown cause. The dose of 10 mg/kg i.v. caused no clinical reactions, but 30 & 100 mg/kg elicited emesis in 1/4 & 4/4 respectively. Clinical reactions at 200 mg/kg & higher were emesis, weakness, defecation, lacrimation, and sometimes conjunctival injection, inactivity, & prone posture at 300 mg/kg. Slight tachycardia occurred at 300 mg/kg, glucosuria & proteinuria at 100, 200, and 300 mg/kg, prominent GOT & GPT at 200 and 300 mg/kg, & hypokalemia at 300 mg/kg. Gross & microscopic exam were reportedly normal.

Rats: The injectable formulation of F when tested for acute i.v. toxicity in mice after exposure to conditions of degradation (2 months at 60°C) displayed an LD50 (410 mg/kg) which was comparable to undegraded material (306-438 mg/kg).

Six analogues of F which are either byproducts of synthesis or products of degradation were tested for acute toxicity. All showed either low toxicity or toxicity comparable to F except for one (A-4) It showed an LD50 of only 113 mg/kg and 225 mg/kg orally in mice and rats and an LD50 i.v. of 22 mg/kg and 18 mg/kg in same. However when a mixture of F and all of the 6 analogues, each analogue at a conc 5 times the expected, the oral LD50 of this mixture in mice was the same as normally manufactured material, i.e. 8000 mg/kg. A-4, which is a byproduct in the synthesis of MK-208, was nephrotoxic in rats treated acutely p.o.

7. IND UNDER WHICH CLINICAL STUDIES CONDUCTED: [redacted]

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B. Subacute Toxicity:

Rats In an i.v. study conducted by Huntingdon Research Groups of 15M and 15F rats were injected daily with 0, 4, 20, 100, or 200 mg/kg of F for 13 weeks.

Results

Clinical reactions following injection were observed in rats injected with 100 & 200 mg/kg. These included tremors, labored breathing, unsteady gait, pallor, and salivation. Survival was reduced at the top dose (4M & 5F deaths). Growth depression & increased water consumption was seen at the upper two levels, as well as anemia and slight increases in urea nitrogen and creatinine (the latter at 200). At necropsy, severe reactions were seen at the injection sites of 200 mg/kg treated animals and renal cortical scarring was seen in 5/15 and 10/11 male rats al 100 & 200 mg/kg. Stomach weights were increased at the upper two levels & adrenal weights in males treated with 200 mg/kg. Microscopic studies confirmed the gross finding in the injection sites at the top dose & the renal effects (foci of basophilic tubules or tubules with flattened epithelium in 3/15, 3/10, 3/10, 7/10, and 11/11 male rats of the C, L, M, + H levels). The concentration of drug used at the top dose was 3.3% (.07 to 1.7% at the lower levels which did not show undue irritation histologically). The stomachs were said to be normal histologically.

Dogs: In a range-finding study conducted by Y beagles were injected i.v. with 0, 100 and 200 mg/kg/day of F for 2 wks. The injection rate was 10 or 20 ml/minute and the conc. of the drug was 2%.

Results: No deaths occurred but distnict clinical reactions were elicited in a dose related way. The reactions were emesis, salivation, conjunctival injection (top dose), collapse (top dose after injection) & associated defecation. No other effect (including biochemical, gross & histological) were seen.

C. Chronic Studies:

Rats

1) In a study conducted by MSD to evaluate the reversibility of eosinophilic cytoplasmic granularity (ECG) of gastric chief cells, groups of 60 male S-D rats were gavaged with 0 or 2000 mg/kg/day of F for 182 days. Twenty rats per group were sacrificed at term (182 days) and the remainder after a 14 wk recovery period.

Results

After 182 days slight ECG of chief cells was seen in 5/24 (21%) controls and 14/20 (70%) treated. After the 14 wk recovery period the incidence was 11/36 (31%) controls and 11/40 (28%) treated, thus indicating reversibility of the effect.

2) A second reversibility study was conducted by Y in two groups of 60 M CRCD rats at oral doses of 0 and 200 mg/kg. Treatment lasted 24 wks & the post-treatment recovery period was 18 wks. Another reversibility study conducted by Y in SD rats entailed the oral administration by gavage of 0 or 2000 mg/kg of F to two groups of 70 to 107 rats for up to 43 wks. Interim autopsies were made at weeks 13, 26, 37 & 39 and at 5 & 13 wks post drug (recovery phase). Subgroups included controls and test animals receiving acid drinking water for 43 wks, at which time they were sacrificed. A fourth reversibility study was done (see below).

Results

In the first study gastric chief cell eosinophilic granularity (ECG) was observed in 10/16 and 11/17 animals treated with 200 mg/kg of F for 14 & 22 wks vs 0/15 & 1/17 controls at corresponding times. Sixteen weeks after discontinuation of treatment in week 24, the incidence of ECG was 1/27 & 1/28 in the treated & controls respectively.

In the second study, the number of incidence ECG cells as cell as the intensity of ECG cell proliferation increased in the drug treated animals as early as 13 wks; these effects intensified over the course of treatment. HCl acid in the drinking water did not prevent or enhance the ECG cell proliferation in the drug treated. There was partial regression of the enhanced number of ECG cells in the test animals 13 wks after cessation of treatment.

In the third study, the ECG cell hyperplasia noted in rats tested for 43 wks was totally reversed 26 wks subsequently.

Dogs:

1) In a 26 week i.v. study conducted by Y groups of 4M & 4F beagles were injected daily with 0, 4, 25, or 100 mg/kg/day. The formulation used was a lyophilized preparation containing L-aspartic acid and dissolved in saline at a conc. of 2%.

Results

One dog at 100 mg/kg collapsed 2 minutes after the first injection & displayed reduced motor activity, decreased respiratory rate, pale mucus membranes & weak pulse. It recovered 3.5 hrs. after injection.

Dose related emesis occurred minutes after injection. Salivation occurred at the top dose as well as reddening of mouth and ears, possibly due to vasodilation , occasionally in 3/8 dogs.

The pulse rate of nearly all high dose dogs was prominently increased 1-3 minutes after injection during the entire study, but were unchanged at the lower doses (5 & 25mg/kg).

No adverse effects were seen in any of the other parameters (water intake, opthalmologic, serum biochem, hematology, myelographic, urinalysis). Injection sites were not unduly affected.

2) In a study identical to the previous one, groups of beagles were injected with 0, 5, 25, or 100 mg/kg for 26 wks; this study was conducted by Shin Nippon Labs.

Results

The results of this study were essentially identical to the previous one. The only notable differences was the presence of mucosal reddening (vasodilation) & slight tachycardia at the 25 mg/kg level as well as at the top dose and the absence of collapse of any treated dog.

D. Reproduction Studies:

1. Fertility & General Reproductive Performance: In a study (#81106) conducted by Y groups of 24M & 48F Sprague-Dawley rats were gavaged daily with 0,500, 1000, 12000 mg/kg for 12 weeks prior to mating & through mating in the case of the males & for 2 wks before mating, through mating & up to day 13 of gestation for 1/4 of the females, or up to day 20 for 1/2 of the females, or through natural delivery & up to weaning for 1/4 of the females. The development & reproductive capacity of the F1 generation was determined & the early growth of the F2 generation. Teratogenicity was determined by examination of the offspring delivered surgically at day 20 of gestation for gross, visceral, and skeletal defects.

Results

None of the test doses produced drastic impairment. Treated responded essentially like controls with respect to mating performance, fertility, fecundity, growth, development & fertility of the F1 generation, and status of the F2 generation. Nor was there any indication of teratogenicity, although the drug appeared to cause minor skeletal variations (increased ribs, sternebrae, and caudal vertebrae). The only offspring that was grossly deformed was a low dose pup with a vestigial tail.

Effects possibly due to F were increased neonatal deaths at the top dose & depressed growth of nurslings at upper two levels.

2) Fertility study #2. In an i.v. fertility study conducted by IRDC, groups of 25 M & 25 F Charles River rats were injected once daily for 60 days before & through mating for the males & for 14 days before mating & up to day 7 of gestation for females with 0, 30, 100, and 200 mg/kg. Offspring were delivered surgically on day 20 & examined for gross, visceral, & skeletal defects.

Results

Male & female fertility as well as in utero development of offspring were unaffected at all test levels. There was no indication of teratogenicity.

The only signs of toxicity were 5 male deaths at the mid dose and 8 males and 1 female at the top dose, all temporally associated with injection. Males seemed to be more sensitive to the drug. Finally, post-dose tachycardia was present in high dose males. Growth of males & females was reduced slightly at the higher levels.

3) Teratology Studies in Rats:

a) In a preliminary dose-range study (#80103) conducted by Y, groups of 12 pregnant C-R rats were dosed orally by catheter with 0, 500, 1000, or 2000 mg/kg of F during days 7-17 of gestation. One half of the animals were delivered surgically on day 20 and the remainder were allowed to deliver naturally.

Results

In this dose range-finding study, F was essentially without effect. The only questionable findings were in the group that delivered naturally & included slight increase in length of gestation at the low & high doses, slight reduction in live birth rate and delivery rate at the top dose. Since the number of animals used per group was small, and since the results in the caesarian group were normal, the few disturbances seen in the group that delivered naturally may not be drug related.

b) In an i.v. Teratology Study conducted by Yamanouchi groups of 30-37 pregnant C-R rats were injected i.v. with a 2% sol. of F at doses of 0, 30, 100, and 200 mg/kg during days 7-17 of gestation. Two thirds of the dams were delivered surgically on day 20 and the remainder were allowed to deliver naturally. The F1 offspring were examined for gross, visceral, and skeletal defects & those delivered naturally were allowed to reproduce.

Results

F caused clinical reactions at 10 and 200 mg/kg (ataxia, piloerection, reduction in motor activity, bradypnea, prostration) associated with injection. Three of 37 dams died at the top dose. Reproductive parameters were essentially undisturbed by all test doses of F. The only suggestions of reproductive impairment were slightly impaired growth of the male & female F1 offspring at the top dose, and slight reduction in the fertility of the F1 high dose animals. There was no evidence of teratogenicity (rate of terata low & comparable in all groups).

4) Teratology Studies in Rabbits:

a) Dose range-finding study by Yamanouchi in non-pregnant rabbits: Groups of five N.Z. White rabbits were gavaged once daily with 0, 500, or 2000 mg/kg of F for 14 days.

Results:

All rabbits survived but both dosages produced distinct toxicity, e.g. growth depression at the low dose & weight loss at the top dose, corresponding reductions in food consumption and dose related reductions in the absolute and relative weight of the liver. There were no clinical reactions & necropsy resealed no gross abnormalities of the thoracic and abdominal organs.

b) Dose range-finding study in pregnant Rabbits:

In the first study (#80106), groups of 8 pregnant N.Z. white rabbits were intubated once per day with 0, 200, 500, 1000, or 2000 mg/kg of F during days 6 to 18 of gestation.

In a second study (# 80111), groups of 5-8 pregnant N.Z. White rabbits were intubated with 0, 50, 100, or 200 mg/kg of MK-208 during days 6-18 of gestation. In both studies, animals were sacrificed on day 29.

Results

In the first study, F exerted toxic effects at all levels. This included abortions in 2/7 at 200 mg/kg, 4/6 at 1000 mg/kg, and 3/6 at the top dose. These abortions occurred six to eleven days after cessation of treatment on day 18 of gestation. Growth was depressed in a dose related way at all levels; growth was depressed during time of drug administration (days 6-18 of gestation), but continued to deteriorate after cessation of drug administration (days 18-29 of gestation). The dams experienced a mean weight loss at all dose levels.

Food consumption was depressed at all drug levels in a dose related way, more so after the period of drug administration. Necropsy revealed yellowish-brown livers in 3 dams at 200 mg/kg and 1 case each at the other drug levels.

There was a dose related reduction in the weight of the fetuses and of the placentae. There was also an increase in dead fetuses in the test groups. Gross anomalies were present in 1 each at the 2000 mg/kg and 1000 mg/kg (in each case included flexion of the left fore-limb) and in 6 from one litter at 500 mg/kg level (2 general edema & 4 edema of head region). Skeletal variants were absent but visceral anomalies included 2 cases of gall bladder defect at 200 mg/kg & one at 1000 mg/kg and one case of bifurcation of the cardiac apex at 2000 mg/kg.

In the second study, growth and food consumption were essentially unaffected up to 100 mg/kg; at 200 mg/kg, growth was depressed slightly.

No drug related deaths or abortions occurred. Whereas none of the 58 control fetuses showed anomalies, three of 46 high dose pups showed anomolies exencephaly, cleft palate, open eyelids & cataract in one, agenesis of the gall bladder with or without rib bifurcation in 2 others).

c) Rabbit Teratology Study (# 81101) by Yamanouchi)

Groups of 9-14 pregnant N.Z. white rabbits were intubated daily during day 6-18 of gestation with 0, 30, 200, or 300 mg/kg and sacrificed on day 29. Offspring were examined for external, visceral, and skeletal defects.

Results

The doses of 30 and 200 mg/kg were essentially without adverse effect. The only disturbances possibly related to drug administration were a transient mild depression of body growth at the beginning of drug treatment at 30 & 200 mg/kg, a slight increase in percent stillbirths at same (12 and 9% at L & M vs 7% in controls), and a reduction in the percent of lumbar ribs (28% vs 43% in controls). One mid dose mother aborted following severe anorexia & weight loss but this dam also showed evidence of accidental intubation at necropsy. The top dose was clearly toxic, causing severe anorexia & growth depression, 4 abortions (3 of which followed severe anorexia & weight loss), a distinct increase in stillbirths (16% vs 7% in controls) with a corresponding slight reduction in avg. live litter size, yellowish liver (fatty metamorphosis) most likely secondary to starvation in five dams. There were no external anomalies at any dose, but 2/77 pups at the high dose showed bent ribs and there was a decrease in the number of lumbar ribs in offspring from the upper two levels as well as a decrease in number of sacrocaudal vertebrae at the high dose. The latter variations reflect delayed ossification and are likely secondary to poor nutrition. The anorexia & weight loss which appeared during treatment with 500 mg/kg of F persisted and in some cases intensified after cessation of drug treatment on day 18 of gestation. All of the four abortions at the top dose occurred after discontinuation of drug treatment and in 3/4 cases was related with severe growth depression.

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d) Intravenous dose range-finding studies in rabbits:

In three non pregnant rabbits, an acute I.V. dose of 100 mg/kg was non-lethal, but 200 mg/kg killed 1/3 and 400 mg/kg killed 2/2.

A study conducted by Yamanouchi utilized 2 groups of 3 pregnant N.Z. White rabbits injected I.V. with 50 or 200 mg/kg of F during days 6-18 of gestation. Reproduction was not drastically impaired, but one dam injected with 50 mg/kg aborted on day 27 and one pup from the top dose showed fusion of the 2nd and 3rd vertebrae. Clinical reactions, e.g. decreased activity & decreased muscle tonus occurred at the top dose only.

e) Intravenous Teratology Study in Rabbits (Study #81107 by Yamanouchi).

Groups of 13-14 pregnant N.Z. White rabbits were injected I.V. during days 6-18 of gestation with 0, 10, 30, or 100 mg/kg of F. After sacrifice on day 29, offspring were examined for external, visceral, and skeletal defects.

Results

None of the test doses produced significant disturbances of reproduction. But growth was somewhat depressed (no weight gain) at the low & mid doses and the percent of empty implantation sites was increased at the same doses. Two abortions occurred at the low dose to dams that showed only mild growth depression. The absence of a dose related relationship raises some doubt whether the aforementioned effects were causally related to the drug.

There was no clear evidence of teratogenicity; isolated anomalies observed in offspring of the test groups were retroesophageal right subclavian artery in one low dose pup, fusion of the 1st & 2nd thoracic vertebra & fusion of the 1st & 2nd rib in one low dose pup, fusion of 7th cervical vertebra and 1st thoracic vertebra with associated vertebrae body defects in a third low dose pup, and finally abnormalities of the thoracic vertebra & ribs in a high dose pup. These effects were not seen in controls.

f) Effect of oral and I.V. administration of F on food consumption in pregnant rabbits: In this study conducted by Yamanouchi, eleven N.Z. White rabbits were gavaged once daily with 500 mg/kg of F during day 6-18 of gestation and allowed to deliver naturally. After a suitable recovery period, the surviving dams were mated again and the six found pregnant were injected I.V. with 100 mg/kg during days 6-18 of gestation.

Results

In the oral phase, F quickly produced a state of total & persistent anorexia in 5/11 dams with an accompanying significant loss in body weight. Appetite & growth was not affected in the other animals. Between days 20 and 27 of gestation (after drug administration had terminated and while animals were still anorexic) the five dams showing appetite & growth suppression aborted. None of the other dams aborted.

In the I.V. study, no growth or appetite suppression was induced & no abortions occurred. The only fetus malformed was one showing exencephaly from a mother injected with 100 mg/kg I.V.

g) Plasma levels in pregnant rabbits

These groups of 5 pregnant N.Z. White rabbits were treated orally with 30, 200, and 500 mg/kg of F during days 6-18 of gestation. Plasma levels were determined at 2 hrs post drug on days 6, 12, & 18 of gestation and at hrs 6 & 24 on day 18.

Results

F produced a predictable depression of appetite & growth. Plasma levels were increased in a dose related manner at 2 hrs post drug at all times tested. However, they were substantially elevated at 24 hrs post drug only at the 500 mg/kg level, which is the threshold level for inducing abortions orally.

5. Peri - and Post - Natal Studies

a) Groups of 25 female rats were dosed orally from day 15 of gestation to the 21st day of weaning with 0, 100, 500, and 2,000 mg/kg of F. Growth, development, & fertility of the F_1 generation was assessed as well as effects on the F_2 generation.

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4) Reversion Test of purified & crude preparations of C-nitroso-F: Neither the purified nor crude nitrosamine forms of F were mutagenic, with or without metabolic activation, against various strains in the Ames test.

5) Repair Test:

F and cimetidine did not inhibit growth of B. subtili strains M45 and H_{17} up to 10 mg/plate, but tiotidine did slightly at the higher concentrations.

6) Repair Test of F, Cimetidine, & Tiotidine after reaction with nitrite:

After reaction with nitrite, both F & Tiotidine were highly positive (growth suppressing) against B - subtilis strains M45 and H_{17}. Each drug suppressed growth of the recombination repair deficient strain M45 much more than the wild strain H_{17}

7) Repair Test of pure & crude C-nitoso - F

Both forms suppressed M45 & H_{17} at the high concentration of 7320 microgram/plate but supression of M45 was not sufficient to reflect a mutagenic activity.

8) Micronucleus Test in Mice

Mice were treated orally for two days with 0.5, 1, and 2 g/kg, then sacrificed for examination of bone marrow cells. F did not cause chromosomal aberrations judged from the no. of polychromatic RBC's with micronuclei.

9) Mammalian Cell Mutagenesis Assay in chinese hamster lung fibroblasts:

In two separate tests, with or without metabolic activation, F did not induce mutation of Chinese hamster lung fibroblasts in vitro up to a conc. of 10 mM per plate whereas positive controls were active.

10) Mammalian Cell Mutagenesis Assay in Ovary cells:

In two separate assays, with or without metabolic activation, F did not induce mutation of Chinese Hamster ovary cells in vitro up to 3mM/plate whereas positive controls were active.

11) Chromosome Aberration Test in Mice.

Groups of 5 mice were treated orally with acute or subacute (5 days) doses of 50, 100, or 200 mg/kg of F I.V. Twenty four hrs. after the last dose, bone marrow cells were examined for chromosomal abberations. The cells from mice treated acutely or subacutely did not show evidence of significantly increased chromosomal aberrations up to the maximum dose.

F) Special Studies

1) Effect on thyroid:

F administered for 5 wks to groups of 15 male rats at 0, 400, 1000, and 2000 mg/kg, did not affect serum level of thyroid hormones, nor the weight or histology of the thyroid gland.

2) Immunogenicity in mice:

F either alone or complexed to a carrier protein, was injected i.p. into mice. Following injection, no IgE antibody appeared up to 25 days after injection, however the positive control, DNF complexed to protein, produced obvious IgE titers.

3) Immunogenicity in G pigs

Groups of 8 g - pigs were injected s.c. three times at six day intervals with 1 or 10 mg/kg of F. Fourteen days after the last injection, the animals were challenged I.V. with F. No F treated died or showed anaphylactic reactions whereas 3/8 positive controls died.

4) Rabbit Eye Irritation:

Instillation of solutions of F up to 1% and at pH 5.5 caused no irritation to the eye or conjunctiva of rabbits.

5) Rabbit Muscle Irritation:

0.1 ml of 0.001% solution of F in distilled water caused no more irritation than saline & was much less irritating than the same volume of 0.75% acetic acid when injected one time into the vastus lateralis muscle of rabbits.

6) In vitro Hemolysis Test:

The injectable formulation (20 mg of F, 8 mg of L-aspastic acid, 40 mg of D-mannitol dissolved in 2 ml of distilled H_2O) caused no hemolysis in vitro in human or rabbit blood. Likewise, no hemolysis or precipitation resulted when two samples of same were tested on washed human RBCs.

7) Irritation in Dogs:

When the above injectable formulation was administered i.m., I.V., intraarterially, or perivenously to dogs at a dose of 2 ml (containing 20mg of F)one time at separate sites, no undue irritation was observed macroscopically or histologically at 24, 48, or 46 hrs. post-drug. Irritation at each test site was comparable to corresponding saline controls.

8) Infusion Study in dogs:

Groups of 3-4M & 3-4 F beagles were infused I.V. 6 hrs per day for 7 days with a 0.4% injectable formulation of F at doses of 0, 4, 12, & 36 ml/kg/day (equivalent to 0, 16, 48, and 144 mg/kg/day).

Results:

No dogs died & injection sites were not affected. The only indication of toxicity was emesis, hypoglycemia, and slight hypotension at the high dose only.

9) Skin Sensitization in G. Pigs:

Topical application of the injectable formulation of F did not elicit a sensitization reaction in the skin of G Pigs which had been previously treated intradermally & topically with the drug. This model reacted very positively to penicillin.

6) Pharmacology

1) In vitro histamine H_2 receptor antagonism:

In vitro, F inhibited histamine induced tachycardia of the isolated rt. heart of G. Pigs as well as histamine induced relaxation of the isolated rat uterus, showing 10 & 166 times the activity of C respectively. F also inhibited dimaprit induced tachycardia of the isolated G. Pig heart in a non-competitive insurmountable way (unlike C & R which showed competitive surmountable antagonism). In the latter, F was bound rather tightly to the H_2 receptor in contrast to R and C which are removed easily through washing.

F inhibited histamine sensitive adenylate cyclase (and thus cyclic AMP formation) in membrane fragments of g. pig gastric mucosa and hippocampal homogenates of g. pig brain. It displayed a dose related competitive antagonism qualitatively similar but 24 times greater than that shown by C.

Like R, F inhibited in a competitive way the utilization of aminopyrine in isolated gastric glands of rabbits. This response reflected inhibition of gastric secretion.

Finally, F competitively and reversibly inhibited dimaprit induced relaxation of isoproterenol stimulated contraction of isolated g. pig lung strips.

F showed in vitro a lack of effect on responses mediated by H_1 - histamine, beta-adrenergic and muscarinic receptors, or acetylcholine release. It was also inactive in radioligand binding tests relating to dopaminergic, neuroleptic, serotoninergic, adrenergic, cholinergic and purinergic sites.

2. <u>In vivo Antisecretory Activity</u>:

F inhibited gastric secretion in gastric fistula dogs stimulated with either histamine, gastrin, 2-deoxy-D-glucose as well as food and dimaprit in Heidenhain pouch dogs. Activity was seen by both the I.V. and oral routes. The effect was characterized by a reduction in volume and in acid & pepsin output and to a lesser extent in acid concentration of gastric secretions. Comparative evaluations invariably showed F to be most potent by far, R intermediate, and C the least potent; against histamine stimulation in orally treated dogs, the most sensitive species tested, F was 95 times more active than C & 14 times more active tha.. R on a weight basis & 127 & 15 times as active respectively on a molar basis. The oral and I.V. ED50 of F against histamine evoked gastric secretion in dogs was only 0.03 mg/kg in each case as compared to 2.86 mg/kg & 1.84 mg/kg respectively for C.

The time course of gastric antisecretory effect of F appeared to be somewhat longer than C or R. For example, when single equivalent antisecretory doses of F and R were given orally to histamine stimulated dogs, F exhibited 67% inhibition 24 hours post drug administration vs. only 2% for R By the I V. route however, duration of activity of F against a constant stimulatory dose of histamine in dogs was only slightly longer (1.3) than C.

In Heidenkain (vagally innervated) pouch dogs, F and C both competitively inhibited the secretory response of dimaprit, a specific H2 receptor aganist, whereas both induced an unsuromountable and thus non-completitive antagonism of methacholine and pentagastion.

In gastric fistula cats, F, given s.c., was 38 and 5 times more antisecretory than C and R against histamine and 20 and 8 times against tetragastrin.

In chronic fistula rats, F and C inhibited basal acid output mainly by decreasing acid concentration; both also lowered pepsin output to a lesser extent. F was about 15 times more potent than C. In pylorus ligated rats treated orally, intraduodenally, and I.V., the ED50 antisecretory dose was similar and averaged 0.58 mg/kg.

No tolerance to the gastric antisecretory effect of F was seen in rats and dogs treated orally with subacute doses.

In rats treated p.o. with 3 mg/kg of F for 8 days, and "acid rebound" effect was noted 3 days after stop of treatment. In another study however, this rebound effect did not appear 1 or 3 days after repeated oral dosing of rats with 5 mg/kg b.i.d. for 30 days.

F inhibited cyclic AMP formation in the gastric mucosa of untreated and histamine stimulated rats, but mostly of the latter.

3) Antiulcer Activity;

F inhibited gastric ulcers induced in rats by a variety of agents or procedures (histamine, indomethacin, aspirin, cysteamine, stress, pyloric ligation) as well as or against duodenal ulcers induced with mepirizole. the ED50 of F ranged from 0.17mg/kg to 0.6 mg/kg and potency ranged from 17-44 times that of C. Effectiveness of F was greatest against histamine induced ulcers. Antacid (maolox) enhanced the antiulcer activity of F in rats.

4. Effect on serum gastrin:

In rats in which the acidity of the stomach was maintained through perfusion of HCl, F did not elevate serum gastrin whereas C did at equivalent antisecretory doses. No data are available on serum gastrin levels in animals treated with F alone.

5) Miscellaneous G. I. Effects:

In normal rats, F did not affect the histamine content of the gastric mucosa, but it did lower the mucosal level of endogenous PGE_2 and PGI_2 to a slight extent; C however lowered these prostaglandins to an even greater extent.

F did not influence propulsion of a charcoal meal in mice but it shortened gastric residence time in rats and dogs. In cats, F did not prevent the fall of transgastric electropotential difference which accompanies the administration of aspirin and which is considered to reflect disruption of the gastric mucosal barrier.

6. Cardiovascular Activity:

F exerted no effect on blood pressure, ECG, or respiratory rate in conscious dogs up to 30 mg/kg p.o. In the general toxicity studies conducted in dogs, no ECG or heart rate changes were noted in dogs treated orally with up to 2000 mg/kg b.i.d. for 30 days, up to 1000 mg/kg for 13 weeks, or 500 mg/kg for one year.

In spontaneously hypertensive rats, F had no effect on blood pressure at 10 mg/kg p.o.

Dogs injected I.V. with 1 mg/kg acutely displayed no effect on ECG or heart rate. However 10 mg/kg I.V. caused slight tachycardia and hypotension, and 30 mg/kg caused distinct tachycardia, hypotension, T wave elevation and increased respiration. The I.V. injection of 300 mg/kg acutely induced respiratory arrest, pronounced sustained hypotension, and finally death 20 minutes post drug.

F exerted no effect on the rate or contractility of the isolated G. Pig atrium.

In a six month I.V. toxicity study in dogs at 5, 25, and 100 mg/kg, reddening of mucous membranes possibly due to vasodilatation and significant tachycardia was noted at 100 mg/kg slight tachycardia only at 25 mg/kg, but no cardiovascular effects at 5 mg/kg.

7. Autonomic Reactivity:

Three mg/kg I.V. of F displayed no effect on muscarinic, nicotinic, histaminergic, H, or sympathetic alpha or beta receptors in dogs. It counteracted dimaprit induced hypotension in dogs through H_2 receptor antagonism.

8. CNS and Behavioral Effects:

F did not elicit any oral CNS effects at high oral doses (up to 2000 mg/kg b.i.d.) in mice, rats, rabbits, cats, or dogs other than retching or vomiting in dogs. It had no effect on locomotion or rotarod performance in mice treated with 100 mg/kg p.o., although 100 mg/kg I.V. reduced activity slightly in this species. Further, F had no effect on thiopentol induced sleeping time in mice or hexobarbital induced sleeping time in rats up to 100 mg/kg p.o. or I.V. whereas C prolonged sleeping time.

F had no effect on pentetrazole induced seizure in mice, displayed no non-narcotic analgesia in mice, nor interfered with morphine analgesia.

Doses of up to 10 gm/kg p.o. or 30 mg/kg I.V. had no visible effect on behavior in mice and rats. Further, F had no effect on metamphetamine induced stereotyped behavior in rats while C did have an effect. Condition avoidance behavior in rats was unaffected with up to 100 mg/kg p.o. but it was slightly impaired in squirrel monkeys at 3 and 9 mg/kg p.o. F exerted no EEG effects in immobilized cats up to 10 mg/kg p.o. Hippocampal after discharge in rabbits was unaffected up to 10 mg/kg I.V. or in cats up to 3 mg/kg I.V., but was delayed significantly in latter at 10 mg/kg. In cats injected I.V. with 3 mg/kg of F, 4% of the plasma concentration of drug was detected in cerebrospinal fluid. In dogs, a dose of 100 mg/kg I.V. elicited vomiting which was not preventable by metoclopramide.

9. Drug Interaction

In Vitro:

F and R demonstrated significantly less binding to Cytochrome P450 than C. In keeping with this, F and R did not display unusual U.V. spectra with microsomal preparations from uninduced and phenobarbital induced rats whereas, C did. Further, F and R had little effect on in vitro cytochrome P450 activity or Benzphetamine N-Demethylase activity with untreated or phenobarbital stimulated microsomes, whereas, C did. F and R had virtually no effect on the in vitro activity of microsomal 7-ethoxycoumarin O-Deethylase activity with untreated phenobarbital, or 3 MC induced microsomes, whereas C did. F and R did not suppress 16 alpha, 7 alpha, and 6 beta hydroxylases of testosterone in liver microsomes of mice, whereas C did. Finally, F did not inhibit amenophyrine N-demethylase activity and diazepam metabolism in vitro, whereas C did.

In Vivo:

F did not delay the metabolism and excretion of diazepam, warfarin or propranolol in dogs, whereas C did judging from increased half-life, decreased peak plasma concentrations, and greater AUC's of these drugs.

F did not increase the plasma concentration of antipyrine in rats whereas C did significantly.

Sleeping time of pentobarbital was unchanged in rats pretreated with F for 14 consecutive days, but significantly reduced in rats pretreated with phenobarbital, a hepatic enzyme inducer. In addition, the phenobarbital-treated rats excreted more ascorbic acid in the urine and displayed larger livers than the F treated rats.

F did not affect hexobarbital sleeping time in rats, whereas C did so significantly.

10. Anti-androgenicity:

Castrated rats supported with exogenous testosterone showed no reduction in prostate or seminal vesicle weight when treated with 50 mg/kg p.o. of F for 7 days. The same model however showed significant reduction in the weight of these organs when treated with the same dose of C.

F did not inhibit in vitro the binding of testosterone to the androgen receptr present in the rat prostate cytosol.

11. ADME

a. Absorption

About 30-40% of an oral dose is absorbed in rats, dogs, and humans. In bile cannulated rats, 28% of an oral dose was recovered in the urine, 2.4% in the bile, and 70% in the feces. Hence, the bioavailability of F is moderate.

The bioavailability of type A crystals present in bulk material was essentially the same as type B crystals (presumably the early pilot batches).

In vitro, 21 to 27% of drug is bound to plasma protein in rat, dog, and human blood. In vivo, 15 to 22% of either F, C or R are bound to protein in the blood of human recipients.

In rats, the 1/2 life after oral dosing was 1.9 hour; peak plasma concentration was reached in about 2 hours.

In humans and dogs treated p.o. the half life was about 3 hours and the peak plasma concentration was reached in 3 hours.

Repeated p.o. or i.v. dosing of dogs showed no tendency for accumulation in the plasma.

b. Distribution:

In rats treated orally with a single dose, the levels of F were highest in the G.I. tract, kidneys, liver, submandibular glands, and pancreas in descending order. After i.v. administration the same order of distribution was found except that none was present in the G.I. tract. Little if any was found in the brain in either instance. All evidence of drug was absent by 24 hours post-drug.

Whole body radiographic studies of acutely-treated rats revealed only trace amounts after oral dosing (exclusive of the G.I. tract), but significant amounts in the liver, kidneys, G.I. tract, arteries, epiphyseal membranes, fasces, and uvea after i.v. dosing; drug disappeared in a short period of time and none was ever present in the brain or spinal cord.

Administration of drug p.o. or i.v. to pregnant rats showed only traces in fetal tissue, but significant amounts in the milk.

Multiple dose testing of rats for 21 days revealed slight rise in tissue levels of drug, but no significant accumulation; excretion pattern after 21 days (20% in urine and 70% in feces) was similar to that after acute dosing. Virtually no drug was detected in the brain.

Young rats injected i.m. with F from day 1 to day 28 of lactation showed relatively high levels of drug in tissues originally, brain included, but diminishing levels with time. Content of the brain was always less than that in other organs and nil after day 21. The descending order of distribution was kidney, liver, blood, heart and brain.

Young suckling rats nursing from mothers treated p.o. or i.v. on day 14 of lactation showed drug in liver and kidneys but none in the brain.

c. Metabolism:

Metabolism is very similar in rats, dogs and humans in that in each case 80% of absorbed drug is unmetabolized, the remaining 20% being metabolized to one specific product, the S-oxide. Almost all of the absorbed parent compound and its S-oxide derivative are excreted in the urine in each species. The structure of the S-oxide, which incidentally exhibits 1/270th the H_2 receptor antagonism of the parent, is as follows:

Famotidine S-oxide
(identical to F except for O attached to S atom)

the relative immunity of F to metabolism suggests that it will be virtually unaffected by hepatic first pass effect.

d. Excretion:

Excretion of F in rats, dogs, and humans is essentially the same. In each case virtually all of the absorbed drug is eliminated by the kidneys, a very small fraction being eliminated through the bile. This is true whether the drug is given p.o. or i.v.

12. Miscellaneous:

F had no effect on pancreatic or biliary secretion, hepatic blood flow, spontaneous G.I. motility, methacholine induced salivation, immediate hypersensitivity reactions, cellular or humoral immune responses or histamine induced asthma in guinea pigs.

Evaluation:

Famotidine (F), which is structurally related to tiotidine, has been clearly shown from pharmacological assays in vitro and in animals to be a very potent and very selective H_2 receptor antagonist and gastric antisecretory agent. Less certain is that the drug acts on the gastric H_2 receptor in a competitive way like cimetidine (C) and th[illegible] somewhat longer acting in vivo.

In all of the assays, in vitro and in vivo, and regardless of route (p.o. or i.v.) or the secretory stimulant, F was invariably many times more potent than cimetidine(C) or ranitidine (R). For example, against histamine induced gastric secretion in dogs, orally administered F was 95 and 15 time more effective than C and R respectively. The single oral antisecretory ED50 dose of F in the latter model was only 0.03 mg/kg, which is 1/33 the human dose.

The nature of the antagonism was competitive against some H_2 receptors, non-competitive against others. For example, in assays involving gastric receptors (inhibition of dimaprit induced gastric secretion in Heidenhain pouch dogs, inhibition of adenylate cyclase activity and cyclic AMP formation in membrane fragments of guinea pig gastric mucosa), F displayed competitive inhibition qualitatively like that shown by C. However, in an assay that involved non-gastric H_2 receptors (inhibition of dimaprit induced tachycardia of the isolated guinea pig heart), F showed distinct non-competitive and unsurmountable antagonism, whereas C and R showed competitive easily reversible antagonism. In addition, F was shown to be tightly bound to the H_2 receptors in this model while C and R were loosely bound. Since F was always a competitive inhibitor in assays involving gastric systems, it is assumed that it will exert a competitive type antisecretory action in man similar to that observed with C.

The time course (duration) of gastric antisecretory activity of F was somewhat longer than R and C. For example, 24 hours after the oral administration of equivalent antisecretory doses of F and R to histamine stimulated dogs, 67% inhibition still remained with F, but only 2% with R. However, by the i.v. route in histamine stimulated dogs, the duration of antisecretory effect of F was only 1.3 times longer than C. It would appear then that F will be somewhat longer acting than R or C, but not extraordinarily so like omeprazole; 24 hour achlorhydria resulting from a single dose of F is quite unlikely despite the drug's remarkable potency.

The selectivity displayed by F was truly outstanding; whereas, only 0.03 mg/kg was required to demonstrate significant inhibition of gastric acid secretion in histamine stimulated dogs, hundreds times that dose showed no properties indicative of an H_1 receptor antagonist (conventional antihistamine), an anticholinergic or cholinergic, a histaminergic, an alpha- or beta-agonist or antagonist, a CNS stimulant or depressant, a tranquilizer, a behavior altering agent, or an allergenic compound. No cardiovascular or ECG effects were apparent in dogs after an oral dose of 30 mg/kg (1000 times ED_{50}).

Most incredible was the total absence of overt clinical reactions or serious toxicity in rats and dogs treated orally by gavage for 4 to 13 weeks with up to 2000 mg/kg b.i.d., a level which exceeds the ED50 in dogs by a factor of 133,333!

Based on the preclinical findings, F will quite likely be devoid of anti-androgenic properties and not be prone to serious drug interaction problems. For example, like R, and unlike C, F did not bind significantly to cytochrome P450 enzymes of the liver in vitro and did not alter the pharmacologic activity, metabolism, or excretion of a number of C sensitive drugs (diazepam, warfarin, propranolol, pentobarbital, hexobarbital and antipyrine). Concerning anti-androgenicity, F did not influence the effect of exogenous testosterone in castrated rats, interfere with the in vitro binding of testosterone to androgen receptors, or reduce prostate or seminal vesicle weights in rats or dogs treated subacutely with up to 2000 mg/kg b.i.d.

We have no information in animals whether F elevates serum gastrin through induction of gastric hypoacidity. All that has been shown is that F does not increase serum gastrin in rats in which gastric acidity is kept normal by acid perfusion; this contrasts with C which raises serum gastrin under the same conditions.

One striking feature of the pharmakinetics of F is the almost identical way rats, dogs, and humans handle the drug. In all three species, F is moderately absorbed (30-40% of dose) is 20% bound to plasma protein, achieves peak plasma concentration in 2-3 hours, is slightly metabolized to just one metabolite, the S-oxide of the parent compound, and is almost all exereted via the kidneys (98% of absorbed drug via kidneys 2% via bile). This suggests that the pharmacological and toxicological results in animals are probably reasonably reflective of the drug's clinical potential.

The distribution studies showed the customary high concentrations in the kidneys and liver and negligible amounts in the brain and fetal tissue, but one peculiarity was the finding of high amounts of drug in the milk of lactating rats. This may explain why the growth of their nursing offspring tends to be depressed. Another noteworthy finding was the demonstration that, in newborn rats injected i.m. daily for 28 days, F passes the blood-brain barrier with decreasing efficiency until the 21st day, after which time no drug passes the barrier.

Concerning toxicity, the Yamanouchi Company and MSD have together supplied a wealth of animal toxicity data: acute studies in two species by all routes, numerous subacute, chronic, and reproduction tests by the oral route, oral carcinogenicity studies in mice and rats and a large battery of various mutagenicity assays.

As a whole, these data show F to be an astonishingly non-toxic and paradoxically inert compound, especially when one considers its extraordinary antisecretory potency (oral gastric anti-secretory ED50 in dogs is just 0.03 mg/kg and the daily human dose is only 1 mg/kg). For example, the acute oral LD50 of F in mice and rats was in the order of 4000 mg/kg when given in solution form and 8000 mg/kg in suspension form. In multiple dose studies, rats tolerated as much as 2000 mg/kg b.i.d. for 13 weeks and 1000 mg/kg for one year while dogs tolerated as much as 2000 mg/kg b.i.d. for 30 days and 500 mg/kg for one year. In these studies with doses far in excess of the HD, F appeared to be a rather inert compound in that it elicited no overt clinical reactions and no dramatic disturbances. The only indications of drug toxicity were proteinuria in rats and dogs at high doses, occasional elevations of SGPT in dogs, and alteration of chief cells, enlargement of the nuclei of these cells, and finally an increase in eosinophilic cytoplasmic granularity (ECG) of these pepsin secreting cells. Examination with electron microscope revealed only an increase in the density of these granules over that seen in the untreated animal. The threshold dose for this effect appeared to be about 2000 mg/kg p.o. and it was completely reversible within 16 weeks upon discontinuation of treatment. The sponsor conjectures that these chief cell changes may reflect reduced turnover of pepsinogen secondary to the drug's antisecretory effect, but this is difficult to reconcile with the observation that the drug still elicited these changes in rats subjected to continuous HCl perfusion of the stomach. However, the changes did not involve a change in the intracellular concentration of pepsinogen or ability of the cell to secrete pepsin.

One effect that was surprisingly absent in all of the animal studies was ECL cell hyperplasia in the gastric fundus. This gastrin dependent effect is characteristically seen in animals, especially rats, with potent long-acting gastric antisecretory agents (omeprazole, SKF-93479, Loxtidine, and BL-6341A). Perhaps F did not produce ECL cell hyperplasia because, despite its extraordinary potency and somewhat greater duration of action, its time course of antisecretory effect is still incapable of inducing sustained (24 hr.) achlorhydria and hypergastrinemia or anything comparable to it. This of course is a favorable finding because it tends to rule out a potential for inducing gastric carcinoid tumors which arise from hyperplastic ECL cells.

The various mutagenicity tests conducted on F showed it to be lacking in mutation potential. Following reaction with nitrite however, the reaction product (which likely included nitrosamines) was mutagenic against B subtilis strains M45 and H17.

The significance of the latter finding is doubtful however, since F was completely without carcinogenic potential in an oral carcinogenicity study of 92 weeks in mice and 106 weeks in rats up to 2000mg/kg/day in each case. Specifically, there was no evidence of gastric mucosal metaplasia, dysplasia, or neoplasia; there was no sign of the adenocarcinomas which appeared in the pylorus of rats treated for 6 months or more with structurally related tiotidine; nor was there any mention of ECL cell hyperplasia or carcinoid tumors in the gastric fundus. Finally, no carcinogenicity was suggested in any other organ, testes and liver included.

The reproduction studies conducted in animals provided essentially favorable results. Disturbances of reproductive parameters occurred only at high levels and appeared to be related to the sustained appetite suppressant properties of the drug. For example, the drug induced significant anorexia and sustained growth depression in pregnant rabbits at 200 mg/kg p.o. and above (but not at 100 mg/kg, 100 times HD). Some of the mothers that showed significant growth suppression at 200 mg/kg or above aborted their young and showed yellow livers at necropsy; also, the offspring of dams that did not abort gave birth to offspring that weighed less than corresponding controls. These effects, particularly the abortions, are no doubt indirectly due to prolonged starvation and not directly due to the drug. Supporting this is the fact that abortion never occurred during the drug treatment period, but later, (in the interval that separated termination of drug treatment and planned time of sacrifice of the mothers), and after virtual total anorexia had been in effect for some time. Also, abortion rarely occurred in a rabbit that did not show significant growth suppression.

Another disturbance possibly related to anorexia was the extended impaired growth of nursing neonatal rats. As suggested earlier, this may be attributed to the demonstration that F passes the blood-mamary gland barrier with ease in this species and accumulates in the milk and in addition passes the blood-brain barrier of neonates with relative ease for the 1st 21 days. The threshold maternal dose for neonatal growth depression was about 500 mg/kg. The persistence of the anorexia associated with F was reflected by the fact that weaned offspring continued to show growth depression for some eight weeks after separation from treated mothers.

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In summary, based on the animal findings, Famotidine is predicted to be a very potent, very selective, long-acting and competitive H_2 receptor antagonist. The data also predict an unusually safe compound with a therapeutic index superior to cimetidine or ranitidine. It will likely compare to ranitidine and contrast with cimetidine in being devoid of anti-androgenicity and significant drug interaction complications. It should be like cimetidine and ranitidine and unlike metiamide in lacking a significant potential for agranulocytosis. Freedom from cardiovascular complications with oral use may be a unique advantage for F. Despite its extraordinary potency and somewhat longer duration of action, Famotidine does not seem to have any potential to cause sustained gastric achlorhydria, sustained hypergastrinemia, gastric ECL hyperplasia, or gastric carcinoids when administered once a day regardless of dose. In oral carcinogenicity studies of approximately 2 years duration in mice and rats up to 2000 mg/kg, (2000 times HD), it demonstrated no carcinogenic potential in any organ, the stomach, liver, and testes included.

In conclusion, Famotidine has been thoroughly investigated in animals and has clearly demonstrated efficacy and reasonable safety. Accordingly, this well-organized and very readable NDA (#19-462)by Merck Sharpe and Dohme for Pepcid(famotidine) Tablets is approvable from the preclinical standpoint.

The only recommendations offered are that the labeling:

1. warn against use by nursing mothers since in rats Famotidine accumulates in the milk, penetrates the blood-brain barrier of neonates with relative ease, and causes extended growth depression in nursing offspring.

2. suggest lowering of dose in patients with impaired kidney function since in rats, dogs and humans, absorbed drug is eliminated almost exclusively in the urine.

Pierre Deslauriers
Pierre Deslauriers, Pharmacologist

cc: Orig. NDA 19-462
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NOV 1 1984

September 13, 1984

Review and Evaluation of Animal Data
(Amendments of April 6, 1984)

The amendment supplies the following additional animal date:

1. Three month range-finding study in mice: Groups of 15 M and 15 F mice were gavaged once daily with MK-208 at levels of 0, 100-200, 400 700-1500, and 1000 mg/kg for 3 months in a study intended to find suitable doses for a carcinogenicity study.

   Results:

   Due to lack of toxicity, some dose levels were increased at five weeks. Viscosity limited the maximum dose to 2000 mg/kg. The drug was apparently very well tolerated at all levels, survival and growth being undisturbed. Necropsies were not done.

2. Ninety two week carcinogenicity study in mice: Groups of 50 M and 50 F Charles River mice were given MK-208 in suspension by gavage once daily at levels of 20, 200, and 2000 mg/kg/day (2000 times the daily human dose) for 92 weeks.

   Results:

   All treated groups performed as well as controls, the treated were like controls with respect to survival, growth, ophthalmoscopic exams, and gross and histologic findings except that diffuse distention of the glands of the fundus of the stomach was noted in 42% of the females at the top dose vs 11% among controls. There was no specific tumor that was statistically more prevalent in the test groups vs controls. There was no indication of carcinogenicity in either the stomach or testes. The only suspect finding was the occurrence of adenoma or adenocarcinoma of the lung in 31 of 100 low dose animals vs. 22/100 and 15/100 in the two control groups; however, the incidence at the mid and high dose was like the controls.

3. One hundred and six week carcinogenicity study in rats: Groups of 50 M and 50 F rats were gavaged with 20, 200, and 2000 mg/kg of MK-208 in suspension for 106 weeks. Two control groups each of similar number were used.

NOV 1 1984

September 13, 1984

Review and Evaluation of Animal Data
(Amendments of April 6, 1984)

The amendment supplies the following additional animal date:

1. Three month range-finding study in mice: Groups of 15 M and 15 F mice were gavaged once daily with MK-208 at levels of 0, 100-200, 400 700-1500, and 1000 mg/kg for 3 months in a study intended to find suitable doses for a carcinogenicity study.

   Results:

   Due to lack of toxicity, some dose levels were increased at five weeks. Viscosity limited the maximum dose to 2000 mg/kg. The drug was apparently very well tolerated at all levels, survival and growth being undisturbed. Necropsies were not done.

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   Results:

   All treated groups performed as well as controls, the treated were like controls with respect to survival, growth, ophthalmoscopic exams, and gross and histologic findings except that diffuse distention of the glands of the fundus of the stomach was noted in 42% of the females at the top dose vs 11% among controls. There was no specific tumor that was statistically more prevalent in the test groups vs controls. There was no indication of carcinogenicity in either the stomach or testes. The only suspect finding was the occurrence of adenoma or adenocarcinoma of the lung in 31 of 100 low dose animals vs. 22/100 and 15/100 in the two control groups; however, the incidence at the mid and high dose was like the controls.

3. One hundred and six week carcinogenicity study in rats: Groups of 50 M and 50 F rats were gavaged with 20, 200, and 2000 mg/kg of MK-208 in suspension for 106 weeks. Two control groups each of similar number were used.

Results:

Again the test groups performed like controls. Morbidity among the males was slightly higher than controls at each test level and among the females as well at the top dose. For example, the percent of rats that died or were sacrificed before termination was 64%, 76%, 78% and 76% among the C,L,M, and H dose males and 42%, 48%, 52% and 72% among the respective females. Some of these deaths in the test groups were most likely due to accidental lung intubation considering the higher incidence of foreign body material in the lungs of animals at the upper two levels. Growth was unaffected and ophthalmoscopic exams were normal. Gross and histologic exams did not show carcinogenicity in any organ, the stomach and testes included. The only questionable finding was endometrial polyp in 3/50, 1/50, and 1/50 females at the high, mid, and low doses vs 0/100 control females, this tumor however was not statistically significant.
Non-neoplastic changes that were drug related included: glandular tissue distention in 5/50, 3/50, and 10/50 females from the low, mid and high dose levels vs 1/100 control females, nuclear enlargement of glandular mucosa in 9/100 and 26/100 from the mid and high doses vs 7/200 controls, eosinophilic cytoplasmic granularity of zymogen chief cells in 23/100 and 49/100 from the mid and high doses vs 25/200 controls. The sponsor considers all of the foregoing changes as "physiologic alterations related to the pharmacologic activity of the test article, i.e. inhibition of pepsin turnover secondary to inhibition of acid secretion".

EVALUATION:

The ninety two week carcinogenicity study in mice and the 106 week carcinogenicity study in rats did not show MK-208 to be carcinogenic in either species tested approximately two yrs. with daily dosages ranging up to 2000 mg/kg or 2000 times the human dose of 1mg/kg/day. It was notable that there was no evidence of carcinogenicity in either the stomach or testes.

Because some H2 receptor antagonists have produced stomach and testicular tumors near the end of a rodent's lifetime, it would have been preferable if these studies were lifespan studies. Since however they gave not even a suggestion of tumors in either organ after a fairly lengthy period of time (which extended over most of the animals' lifespan), the submitted studies appear to reasonably exclude the possibility of carcinogenicity.

Pierre Deslauriers

Pierre Deslauriers, Ph.D.

cc:Orig
HFN/110
HFN/110/CSO
HFN/110/PDeslauriers
cb/10/22/84/8628c
R/D: C.A.Resnick
Dr Bachrach
Dr. Stern

NDA 19-402

D. Conclusions and/or Recommendations

The NDA can be approved from a chemistry standpoint.

CHRiggleman
Reviewing Chemist

NDA 19-402
HFD-160
Doc. Rm. 160
R/D CHRiggleman 12/15/88
R/D init by GPoochikian 12/15/88
F/T LSturdivant 12/16/88
Wang 2333M Disk 0109M
CSO JIM HANNAN

Stat Rev

N19.462

Statistical Review and Evaluation

NDA #: 19-462/Drug Class: 1C

Applicant: Merck, Sharp & Dohme Research Laboratories

Name of Drug: PEPCID (Famotidine) 40 mg/hs

Indication: For treatment of active duodenal ulcers, gastric ulcers, the prophylactic use in duodenal ulcer disease, and the treatment of pathological hypersecretory conditions such as Zollinger-Ellison Syndrome

Documents Reviewed: Volumes 1.1 and 1.39-1.46 of the NDA submission dated June 24, 1985.

The statistical section of this NDA submitted to the Division of Biometrics contains one domestic (placebo control) and one international (ranitidine control) duodenal ulcer study each of which covers an acute phase followed by a six-month maintenance phase. It also contains an international (placebo control) and a Japanese (gefarnate control) acute gastric ulcer trial. This review will mainly discuss the efficacy results of these trials. The safety aspects of these studies have been covered in detail by Dr. Bachrach/HFN-110, the medical reviewer, and will not be discussed in this review.

Since similar designs and methods of analysis were used in all four studies, they will be described in detail only in the first study.

Domestic Duodenal Ulcer Study

The principal objectives of this study were to determine the clinical efficacy and safety of doses of famotidine in the short-term treatment of active duodenal ulcers and in the long-term maintenance treatment of duodenal ulcer disease.

The acute phase of this study was a multiclinic (34 investigators), double-blind, randomized, placebo-controlled trial lasting 8 weeks. During the initial screening visit (baseline), a complete physical and laboratory examination were performed and pertinent baseline information (e.g., alcohol, smoking, etc.) were obtained. An endoscopy was performed at this time to verify the presence of a duodenal ulcer and to determine the number, size and location of the ulcer(s). The presence of duodenitis or erosions was also noted. The patients selected had a primary diagnosis of active duodenal ulcer confirmed by endoscopy. Patients with a 0.5 to 2.5 cm lesion within the duodenal bulb or pyloric channel who exhibited clinical symptoms of active duodenal ulcer and met admission criteria were permitted to enter the acute phase of the study. Patients were randomized to either famotidine 40 mg/hs, 20 mg/bid, 40 mg/bid or placebo. Clinical symptoms were assessed and endoscopies were performed at Weeks 2, 4 and 8 to verify the healing status of the duodenal ulcer. Ulcers were considered to be healed if no ulcer was present (defined as complete epithelialization of the ulcer). Ulcers with

partial/incomplete epithelialization were considered as not healed. Patients were asked to record daily the occurrences of night and day pains, the number of antacid tablets and the number of doses of the prescribed treatment medication taken. Pains were recorded on the following scale: 0=none, 1=mild, 2=moderate and 3=severe. Patient's daily pain scores for Days 1 to 7 and weekly pain evaluation for Weeks 2 to 8 were recorded by the investigator on the CRF. Adverse clinical experiences reported were volunteered by the patient and were not solicited by the clinicians.

If a patient's ulcer was healed within the 8-week treatment period as verified by endoscopy during one of the three visits, then he was withdrawn from the acute phase and became eligible for re-randomization into the 6-month maintenace phase of the study. Patients whose ulcers had not healed at the end of 8 weeks of therapy were considered as treatment failures and were not considered eligible for the maintenance study. For patients who entered the maintenance phase of the study, endoscopies were done to verify the presence or absence of duodenal ulcers at 3 and 6 months or at any time at the discretion of the clinician when the patient reported symptoms suggestive of the presence of an ulcer. During endoscopy, the presence of duodenitis or erosion was noted by the endoscopists. Adverse clinical experiences reported were volunteered by the patients and were not solicited by the clinician. It appears that pain and symptom data were not systematically collected during this maintenance period. This was not discussed in the statistical section and no pain and symptom data were provided.

Sponsor's Study Results

Acute Phase

A total of 384 patients entered the acute phase and were randomized to the four treatment groups. These treatment groups were generally comparable at baseline with respect to various pertinent patient characteristics such as smoking, ulcer size etc. (see Table 1). During this acute phase, 21 patients were either off drug or violated protocol. Of the remaining 363 patients, 10 had no treatment data and 59 were discontinued due to adverse experience, ineffective therapy or other reasons. There were significantly more placebo patients than famotidine patients among the therapeutic failures in each of the treatment groups.

Efficacy analyses were done on two data sets: the "per protocol" and the "all patients treated" data sets. The former excluded all patients who were either off drug or protocol violators, and the latter included all patients who had baseline and some post-baseline treatment values.

The primary efficacy parameter was the cumulative frequencies of healed ulcers observed via endoscopy at Weeks 2, 4 and 8. Crude healing rates were compared among treatment groups using Fisher's Exact test (see Table 2). In this analysis, dropouts were considered as not healed. The Kaplan-Meier product limit (life-table) estimates of the healing rates were also obtained. This method assumed that dropouts healed at the same rate as those observed for patients who completed the study (see Table 2). Since these results were very similar for the two data sets, only the results based on the "per protocol"

data set are presented here in Table 2. As noted earlier, because the placebo group had significantly more dropouts than the treatment groups, the crude healing rates comparison would tend to be more favorable to famotidine. Therefore, in this case, the Kaplan-Meier product limit estimates would be more preferrable. However, by either methods, the famotidine treated groups all had significantly higher cumulative healing rates than the placebo group at all time points (for example 88%-89% for famotidine vs. 55% for placebo at 8 weeks $p < 0.01$). The relationship between the various concomitant factors and ulcer healing were also assessed. The results from this trial suggested that initial ulcer size, ulcer history, drinking and esophagus condition may significantly affect ulcer healing (See Table 3). Further analysis indicated that the observed differences in healing rates between the famotidine groups and the placebo group were maintained after adjusting for these factors. However, it would be of interest to point out that for this study the observed treatment differences in healing rates were higher among non-drinkers than among drinkers (placebo drinkers appeared to heal better than placebo non-drinkers) and higher among patients with normal esophagus condition than among patients with abnormal esophagus condition (placebo patients with abnormal esophagus condtion appeared to heal better than placebo patients with normal esophagus condition).

Secondary efficacy measures included reduction from baseline in day pain, night pain and antacid consumption. Day and night pains were assessed by median time until pain relief (and no reoccurrence) using the Mantel-Haenszel method stratifying for baseline pain score. The results for the "per protocol" data as shown in Table 4 suggested that the famotidine patients experienced significantly greater pain relief than the placebo patients beginning Day 1 ($p < 0.001$) both in terms of proportion of patients with pain relief and median time until pain relief. Similar results were observed based on the "all patients treated" data. Antacid consumption was evaluated by comparing the proportion of patients in each group who took antacid therapy at Days 1, 2-7 and Weeks 2, 4 and 8 and at any time during the study and by comparing the mean numbers of antacid therapy during Weeks 1, 2, 4, and 8. The results based on "per protocol" data are displayed in Table 5. Generally, antacid usage was significantly less ($p < 0.01$) in the famotidine groups than in the placebo group.

Reviewer's Comments

1. In order to check the internal consistency of the observed treatment differences in healing rates across investigators, centers with fewer than 15 patients were combined into a single pool (accounting for 40% of total). With the exception of a few investigators (mainly due to small sample sizes within treatment groups), the treatment differences remained generally consistent across these investigators; no significant treatment by investigators interaction was detected.

2. The healing data was also analyzed by this reviewer using the Mantel-Haenszel method and the result corroborated the sponsor's finding.

3. The pain data for this study suggested that famotidine provides fast pain relief (starting with Day 1) to duodenal ulcer patients with baseline

pain. The median time to pain relief was significantly shorter among famotidine patients than among placebo patients at all levels of pain severity.

Maintenance Phase

Of the 280 patients (based on "all patients treated" data set) who had a healed ulcer during the acute phase of this study, only 177 patients (from 27 investigators) who had an ulcer healed within the 8 weeks period were re-randomized into three treatment groups (famotidine 40 mg/hs, 20 mg/hs and placebo) during the maintenance phase. These treatment groups were dissimilar at the baseline with respect to age, age at first ulcer, the week in the acute phase when the ulcer was healed, the number of ulcers, duration of ulcer disease, and condition of the stomach (see Table 6).

Ulcer relapse rate was assessed using the Mantel-Haenszel method based on the "per protocol", "all patients treated" and "dropout-included" approaches. Various definitions of the time of relapse, dropout and study completion were used. All these analyses provided essentially the same results. In this review, only the relapse rate analysis using the Mantel-Haenszel method based on the "per protocol" data set will be discussed. The results of the analysis as shown in Table 7 was carried out over the following time points: period 1 (day 1-42), period 2 (day 43-105) and period 3 (day 106 and later). It suggested that the famotidine treated groups had significantly fewer relapses within all three periods (except for period 3 between famotidine 40 mg/hs and placebo) than the placebo group. Moreover, the cumulative relapse rates based on the Mantel-Haenszel method for the famotidine groups were significantly ($p < 0.01$) lower than that for the placebo group at all time points and after 6 months (respectively 30.2%, 26.2% and 69.9%, $p < 0.01$). To account for baseline differences in some concomitant factors and to adjust for factors that were found in this study to have significant relationship to ulcer relapse, statistical models including terms for treatment, concomitant factors, and treatment by concomitant factor interaction were used. In all cases, the significant differences in ulcer relapse rates between the famotidine treated groups and the placebo group were maintained.

Reviewer's Comments

1. Even though patient visits were scheduled at weeks 4, 12 and 24, endoscopies were performed only at weeks 12 and 24 or at any time at the investigator's discretion if symptoms suggested the presence of ulcer. Therefore, the sponsor's choice of the 3 periods may be misleading in the sense that the first period does not correspond to an endoscopy time. Ulcers that were detected during period 1 were most likely to be all symptomatic; however, because of the width of the relative day range, some symptomatic relapses may be included in the second period. In any event, the absence of pain and symptom data did not permit differentiation between scheduled and unscheduled recurrences.

2. Since only data available by the cutoff date of January 7, 1985 were used in the maintenance phase of this study, estimates of relapse rates may be biased in favor of famotidine, because placebo patients with symptomatic

and/or earlier relapses would be more likely to have data available by the cutoff date. For this study, this bias may affect the observed recurrence rates for all three periods, because about 25% of the patients had enrolled for less than 6 months and only about 22% had either completed or had the opportunity of completeing the 12-month study. More detailed information, which may not be available for this study, would be required to assess the magnitude and effect of this bias.

3. Since only patients whose ulcers were healed within 8 weeks during the acute phase of this study were entered into the maintenance phase, these were very selective patients. They tended to be mostly famotidine responsive patients and to have faster healing time. In fact, the sponsor's data indicated that about 80% of these patients were healed on famotidine in the acute trial; moreover, about 85% of these patients had their ulcers healed within 4 weeks.

4. See overall summary at the end for further comments with regard to the design issue.

International Duodenal Ulcer Study

The objective of this study was to compare the clinical efficacy and safety of 3 doses (same as in the preceeding acute study) of famotidine to 150 mg/bid dose of ranitidine in the short-term treatment of acute duodenal ulcers and to determine the clinical efficacy and safety of 20 mg/hs of famotidine in the long-term maintenance treatment of duodenal ulcer disease. The study design was similar to the preceding domestic duodenal ulcer study except with ranitidine in place of placebo in the acute phase. Some pain and symptom data were available in the 6-month maintenance phase of this study. The approach and the methods of analysis were generally the same as those employed in the preceding study.

Sixty-eight investigators from nineteen countries enrolled a total 1031 patients in the 8 weeks acute phase of the study. Of these, 939 had their ulcers healed during the acute phase and only 645 were enrolled into the maintenance phase. The results of this study is discussed below.

Sponsor's Study Results

Acute Phase

During the acute phase of this study, 1031 patients were randomized into four treatment groups: famotidine 40 mg/hs, 20 mg/bid, 40 mg/bid and ranitidine 150 mg/bid. These treatment groups were generally similar with respect to various baseline characteristics (e.g., smoking, drinking, etc.) except for a slight under representation of females in the latter two groups. There were 51 protocol violators and 46 dropouts who were distributed evenly among the treatment groups. The protocol violators were excluded from the "per protocol" efficacy analysis. The crude rates and the Kaplan-Meier estimate of the cumulative healing rates are shown in table 8. The crude healing rates demonstrated that famotidine 40 mg/bid was significantly superior to famotidine 40 mg/hs at Weeks 2 and 4, famotidine at 20 mg/bid was

significantly superior to famotidine 40 mg/hs at Week 4. However, no significant differences were demonstrated among the treatment groups at Week 8. At the end of the study, both 40 mg/bid and 20 mg/bid were significantly better than 40 mg/hs.

Overall, the results suggested that famotidine at 40 mg/bid was significantly more effective than famotidine at 40 mg/hs early on; but this superiority was not maintained by Week 8. The same result may be observed of famotidine 20 mg/bid and ranitidine 150 mg/bid relative to famotidine 40 mg/hs. However, their numerical superiority over the latter (40 mg/hs) did not achieve statistical significance. The difference between famotidine 40 mg/bid and 40 mg/hs remained consistent across various levels of factors such as initial ulcer size, smoking, drinking, number of ulcers and baseline day/night pain which suggested an association with ulcer healing rates These observed differences were not evident within individual investigator or within each country. Indeed within individual investigators with at least 28 patients (only 6 such investigators), no consistent differences between famotidine 40 mg/bid and 40 mg/hs were observed; a significant difference was observed only in the pooled data set consisting of investigators each with fewer than 28 patients. Within the two countries with the most number of patients (German, N=209 and Italy, N=245), there were no significant differences among the treatment groups.

With respect to day/night pain relief and antacid use, all treatment groups reported significant pain reduction from baseline and there were generally no significant difference between treatment groups (see Table 9) except for a significantly longer median time to night pain relief and a significantly greater proportion of patients with antacid usage during the first week observed in the ranitidine group (see Table 10).

Reviewer's Comments

The acute phase of this study was an active (ranitidine)-controlled trial. Therefore, questions concerning whether the observed outcome would have differed significantly from the outcome of a placebo group had one been present and whether the absence of a placebo control would result in a "positive bias" naturally arise. However, from available controlled trial results from the published literature, the sponsor provided reasonable arguments which suggested that famotidine would likely be superior to placebo had one been present (see Vol. 1.47, section L: Special Report).

Maintenance Phase

Of the 939 patients who completed the acute phase of the trial with an endoscopically verified completely healed duodenal ulcer, 645 were re-randomized to either famotidine 20 mg/hs or placebo in the maintenance phase. Assessment of clinical symptoms were made at weeks 0, 4, 12 and 24 with endoscopies performed at weeks 0, 12 and 24. Endoscopy may be performed at the discretion of the investigator at an unscheduled visit when a patient reported symptoms suggestive of ulcer recurrence. The two treatment groups were generally similar with respect to various baseline characteristics except for smoking; the placebo group had slightly more smoking patients (p=0.074).

Duodenal ulcer relapse rate was analyzed the same way as was done in the preceding domestic study. The crude rates and the life table rates (Kaplan-Meier) for the three periods are shown in Table 11. Famotidine 20 mg/hs group had significantly lower relapse rates than the placebo group for all three periods (30% vs 73%, for the 3rd period, $p < 0.01$)

Factors found to be related to duodenal ulcer relapse in this study included smoking, ulcer history, duration of ulcer, onset age, other conditions in the duodenum, week healed in the acute study and antacid use. However, no significant treatment by factor interaction was found. Treatment differences were also found to be consistent across investigators.

Table 12 provides the distribution of day and night pain at baseline and at the end of the study for the two treatment groups (refer also to Medical Reviewer's Table 46). At baseline, 80-90% of the patients had no pain. This reflects the fact that these patients' ulcers had just completely healed at baseline. However, at the end of the study, the proportion of patients with pain (day/night) in the placebo group was significantly greater ($p < 0.01$) than that observed in the famotidine group.

Overall, the proportion of patients who took antacid therapy at any time during the study was significantly higher in the placebo than in the famotidine group (49% vs 33%, $p < 0.01$).

Reviewer's Comments

1. Among those patients who withdrew from the trial, there were more placebo patients (26 vs 7) who dropped out on account of therapy ineffectiveness (exactly what does this mean in a maintenance trial?) and more famotidine patients (41 vs 22) who were lost to follow-up/other reasons. When these patients were assigned the same recurrence rates as observed for the respective treatment groups, similar results were obtained.

2. As in the domestic maintenance trial, the patients enrolled in this maintenance trial were also mostly famotidine responsive patients (75% of these patients were treated by famotidine in the acute phase) and 80% of them had their ulcers healed within 4 weeks during the acute phase.

3. Even though 68% of these patients were enrolled prior to 1984, the bias (see reviewer's comment (2) on the domestic maintenance study) favoring famotidine due to the cutoff date of December 27, 1984 would affect the 3rd period relapse rates in this study.

4. The availability of pain and symptom data in this study ought to provide some useful information concerning scheduled and unscheduled relapse rates and estimate of the bias discussed in Comment (3). However, these data were not readily available in the submission.

International Gastric Ulcer Study

The primary objective of this study was to determine the efficacy and safety of famotidine 40 mg/hs in the short-term treatment of acute gastric ulcer. This was an 8-week double-blind, randomized, multicenter (44 investigators across 14 countries) and placebo-controlled study. Patients with a primary diagnosis of active gastric ulcer between 0.5 and 2.5 cm confirmed by endoscopy were eligible to enter the study subject to some other entry criteria. Assessment of clinical symptoms and endoscopies were performed at weeks 0, 4, 6 and 8. Patients whose ulcers had completely healed by the time of any visit were considered to have completed the study. Patients were instructed to record daily pain occurrences and antacid consumption. Concomitant therapies, antacid consumption and dosage of test drug taken during the study were recorded by the investigator at each visit.

Sponsor's Study Results

A total of 336 patients entered the study. One hundred sixty-seven patients were assigned the famotidine 40 mg/hs treatment and 169 the placebo treatment. Both treatment groups were comparable at baseline with respect to various pertinent baseline characteristics except for drinking habit which was more prevalent among the placebo patients than among the famotidine patients (59% vs 44%, $p < 0.01$).

Both the crude cumulative healing rates and the Kaplan-Meier life-table estimates of the healing rates were significantly ($p < 0.01$) greater for the famotidine group than for the placebo group at weeks 4, 6 and 8 (for example, at 8 weeks, 80% for famotidine 40 mg/hs vs. 54% for placebo, $p < 0.01$, see table 13).

The data suggested significant relationship between ulcer healing and initial ulcer size and antacid use. However, no significant treatment by factor and treatment by investigator interactions were found; the treatment differences were generally consistent across investigators and various factor.

The two treatment groups were similar at baseline with respect to day pain with over 73% of patients having moderate or severe pain. Patients from both treatment groups experienced significant pain relief starting at day 1 ($p < 0.01$) and continue to the end of the study. However, the difference in the proportion of patients with pain relief at any time during the study was only marginally different between treatments ($p=0.06$). However, the famotidine group had a significantly shorter median time to pain relief (14 days vs 35 days, $p < 0.01$). No significant treatment difference was observed in the relief of night pain. There were significant differences ($p < 0.05$) between the treatment groups during the first week in the proportion of patients taking antacid therapy and in the overall mean number of days of antacid therapy (famotidine group was shorter by only a day).

[redacted] Comments

[redacted] for this study appeared to be appropriate. Famotidine [redacted] end of 8 weeks based on both the crude rates

and the Kaplan-Meier life-table estimates. Because of the significantly greater proportion of placebo therapeutic failures ($p < 0.01$), the Kaplan-Meier estimates were more preferrable. However, based on these estimates, the superiority of famotidine over placebo was also significant at weeks 4, 6 and 8 ($p < 0.01$).

Japanese Gastric Ulcer Study (Yamanouchi)

This was an 8-week, multicenter (32), double-blind, randomized, gefarnate-controlled study conducted according to Yamanouchi Pharmaceutical Co.'s protocol. The study compared the efficacy and safety of famotidine 20 mg/bid to that of gefarnate 100 mg/tid in patients with endoscopically confirmed single gastric ulcer of circular or oval shape with at least 0.5 cm in major axis at stage A_1 or A_2 of Sakita and Miwa's 6-stage classification (see Table 14). One hundred ninety-two patients were entered and assigned at random to either famotidine 20 mg/bid or gefarnate 100 mg/tid. Clinical visits were scheduled at weeks 4 and 8. Endoscopies were performed at these visits.

The primary efficacy measure was the cumulative frequencies of endoscopically confirmed ulcer healing as defined by stage S_1 or S_2 of Sakita and Miwa's classification (see Table 14) at each time points (week 4, week 8 and after week 8). A supporting measure was ulcer related pains which were divided into pain after meals, pain in a fasting state, night pain and pain unrelated to meals. Pain was rated by the patients as to its degree: none, mild, moderate and severe.

The crude healing rates and the Kaplan-Meier estimates are displayed in Table 15. The famotidine 20 mg/bid group had significantly ($p < 0.01$) greater healing rates than gefarnate 100 mg/tid group at all time points. The observed treatment difference was generally consistent across various factor levels. Data did not permit the examination of treatment by investigators interaction.

Surprisingly, a large number of patients (40%-70%) had no pain at baseline. The proportion of patients with pain relief during the study was not significantly different between the two treatment groups. However, among patients with moderate and severe pains at baseline, the famotidine group appeared to have shorter median time to pain relief.

Reviewer's

, is equivalent to placebo, then the result of this in support of the efficacy claim for famotidine. rovided in the submission to substantiate this simply for the sponsor to consider them to be mation (well-conducted trials in Japan or ted their equivalence? (Gefarnate is a , but not in the United States.) gefarnate healing rate ling rate of 54% in the U.S. population

(ranitidine trial), one may question whether gefarnate might actually be inferior to placebo (gefarnate < placebo). That is, does gefarnate actually hinder ulcer healing? If this were to be the case, then one cannot conclude from the relation, gefarnate < famotidine, that famotidine is necessarily superior to placebo; and the result of this study would not be able to provide the necessary supportive evidence for the efficacy claim.

Overall Conclusion

1. The acute phase of the domestic duodenal studies demonstrated that famotidine at the doses of 40 mg/hs, 20 mg/bid and 40 mg/bid were significantly more effective than placebo in the treatment of acute duodenal ulcers. The results of the acute phase of the ranitidine-controlled international study together with the arguments advanced by the sponsor provided supportive evidence to the claim that famotidine at these doses were superior to placebo.

2. Because essentially the same design (except endoscopies were scheduled at 3 and 6 months) as used by Glaxo in their ranitidine maintenance trial was employed in the two maintenance studies here, the same design issues may be raised here (See transcript of March 1985, G.I. Advisory Committee Meeting). That is, if famotidine merely relieves symptoms and accelerates healing without actually preventing recurrences then under the present design with scheduled endoscopies relatively infrequent and far apart and with allowance for unscheduled endoscopy for cause, one would expect to observe fewer ulcers in the famotidine treated group. Therefore, it seems one still needs to know how much of the observed difference in recurrence rates may be attributed to
differences between treatments in symptom relief and in healing rates and how much may actually be attributed to differences in relapse rates?

   Without being able to obtain such estimates, one cannot draw an unambiguous inference with respect to the prevention claim based on the results of these maintenance studies. Nevertheless, Dr. Lipicky has indicated that a maintenance claim could still be made if these studies can successfully demonstrate a significant treatment difference in both the observed proportions of unscheduled and scheduled ulcer relapses during the first period (0-3 months). This is based on the reasoning that if these conditions were met, then a patient certainly would benefit from a maintenance treatment because he would experience a relief of symptoms and his ulcers would heal faster, taking into consideration the relatively low safety risk associated with famotidine treatment.

3. Because of the early cutoff date for both the domestic and the international maintenance study, a bias might have been introduced into the observed recurrence rates on account of the fact that more placebo patients with symptomatic relapses would have data available by the cutoff date than famotidine patients. For domestic study, this bias may affect the observed recurrence rates for all three periods because about 25% of the patients had enrolled for less than 6 months and only about 22% had either completed or had the opportunity to complete the 12-month study. For the international study, this bias mainly affects the observed third

period (> 6 months) recurrence rates, because only about 5% of the patients at the time of this NDA submission had enrolled for less than 6 months, while close to 70% of the patients had either completed or had the opportunity to complete the 12-month study.

An accurate assessment of this bias would require more detailed information on symptom data which was not present in the domestic study and was not readily available in the submission for the international study.

In view of the above comments, the sponsor has been requested by this reviewer to provide tables of relapse rates at 3 and 6 months broken down by scheduled vs. unscheduled endoscopy. The sponsor has also been asked to make an assessment of the effect of the bias introduced by the early cutoff date on the recurrence rates in the first (3 months) and second (3-6 months) periods for the domestic study. Of course such assessment would not have become necessary, if the sponsor had submitted their analyses based on the completed studies.

Consequently, based on the available data at hand, one cannot recommend a 6-month maintenance claim for famotidine at the present time. A more definitive statement may be made after the sponsor has provided the above requested information. This will be discussed in a subsequent addendum.

4. The international gastric ulcer study showed that famotidine at 20 mg/bid was significantly superior to placebo at 4, 6 and 8 weeks in healing rates.

   The Japanese gastric ulcer trial demonstrated that famotidine was significantly superior to gefarnate. Even though the sponsor considered gefarnate to be equivalent to placebo, this was not sufficient especially in view of the relatively low healing rates associated with gefarnate treatment. One needs to have well-conducted trial(s) that demonstrate the equivalence of gefarnate and placebo (in a Japanese population?) and show that gefarnate is really no worse than placebo.

Comments Which May be Conveyed to the Sponsor

Because of the flaw in the maintenance study design, one cannot draw an unambiguous inference with respect to the prevention claim based on the data collected from these studies. However, a maintenance claim may be made if these studies can sucessfully demonstrate a significant treatment difference in the observed proportions of unscheduled and scheduled ulcer relapses based on patient population at risk.

[illegible] to be able to make the maintenance claim for 6 months, the [illegible] provide tables and accompanying analyses of relapse rates at [illegible] broken by scheduled vs. unscheduled endoscopy.

Furthermore, because of the bias introduced into the observed recurrence rates at 3 and 6 months in the domestic study due to the early cutoff date, an assessment of this bias would be necessary.

George Y.H. Chi, Ph.D.
Mathematical Statistician

cc:
Orig. 19-462 NDA
HFN-110
HFN-110/Dr. Bachrach
HFN-110/Dr. Lipicky
HFN-344/Dr. Lisook
HFN-713/Dr. Dubey ✓
HFN-713/Dr. Chi
Chron.
File: DRU 1.3.2 NDA
Dr. Chi/x34594/njs/sh/04/01/86/#0442n

Concur: Dr. Dubey 6/4-15-86

TABLE 1
Selected Characteristics of Treatment Groups at Baseline
(Domestic Duodenal Ulcer Study - Acute Phase)

Characteristic		Famotidine 40 mg/hs		Famotidine 20 mg/bid		Famotidine 40 mg/bid		Placebo	
Sex	Male	75	(78%)	69	(78%)	81	(82%)	76	(76%)
	Female	12	(22%)	20	(22%)	18	(18%)	24	(24%)
Smoking	Yes	58	(60%)	52	(58%)	59	(60%)	61	(61%)
	No	38	(40%)	37	(42%)	40	(40%)	39	(39%)
Drinking	Yes	18	(19%)	12	(13%)	14	(14%)	13	(13%)
	No	78	(81%)	77	(87%)	85	(86%)	87	(87%)
Initial Ulcer Size (cm)		0.86		0.91		0.88		0.86	
Number of Ulcers	1	79	(82%)	73	(82%)	88	(89%)	82	(87%)
	2+	17	(18%)	16	(18%)	11	(11%)	13	(13%)
Age at 1st Ulcer Mean		37.9		40.6		35.8		39.7	
Duration of Ulcer (Years)		7.7		6.7		7.8		6.7	
Ulcer History	0	30	(31%)	42	(47%)	34	(34%)	26	(26%)
	1	22	(23%)	19	(21%)	24	(24%)	30	(30%)
	2+	44	(46%)	28	(31%)	41	(42%)	44	(44%)
Esophagus Condition	Yes	24	(25%)	27	(30%)	20	(20%)	33	(33%)
	No	72	(75%)	62	(70%)	79	(80%)	67	(67%)

TABLE 2
Crude and Kaplan-Meier Estimated Cumulative Healing Rates
(Domestic Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Treatment	Type of Estimate	N	Time of Endoscopy Week 2	Week 4	Week 8	End of Study
40 mg/hs	Crude	89	28 (32%)*	62 (70%)*	74 (83%)*	75 (84%)*
	Kaplan-Meier		32%*	72%*	88%*	90%*
	Dropouts		5	3	1	0
20 mg/bid	Crude	84	32 (38%)*	56 (67%)*	69 (82%)*	69 (82%)*
	Kaplain-Meier		38%*	70%*	89%*	89%*
	Dropouts		6	2	1	0
40 mg/bid	Crude	93	32 (34%)*	70 (75%)*	76 (82%)*	77 (83%)*
	Kaplan-Meier		34%*	79%*	89%*	90%*
	Dropouts		5	5	0	0
Placebo	Crude	97	16 (17%)	30 (31%)	44 (45%)	44 (45%)
	Kaplan-Meier		17%	33%	55%	55%
	Dropouts		11	15	4	0

* All rates were significantly higher than the coresponding placeo healing rates ($p < 0.05$)

TABLE 3
Frequency and Percent of Patients with Ulcer Healed
Stratified by Selected Factors
(Domestic Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Factor	Level	Treatment 40 mg/hs	20 mg/bid	40 mg/bid	Placebo
Ulcer size (cm)	0.5-0.9	45/50 (90%)	37/43 (86%)	37/48 (77%)	29/54 (54%)
	1.0-1.4	22/28 (79%)	18/26 (69%)	26/30 (87%)	13/31 (42%)
	1.5-2.5	8/11 (73%)	14/15 (93%)	14/15 (93%)	2/12 (17%)
Ulcer History	None	26/29 (90%)	34/40 (85%)	27/31 (87%)	14/25 (56%)
	Single	18/22 (82%)	16/19 (84%)	19/23 (83%)	15/29 (52%)
	Multiple	31/38 (82%)	19/25 (76%)	31/39 (80%)	15/43 (35%)
Esophagus Condition	Normal	56/67 (84%)	47/57 (83%)	62/76 (82%)	25/66 (38%)
	Abnormal	19/22 (86%)	22/27 (82%)	15/17 (88%)	19/31 (61%)
Drinking	No	59/71 (83%)	58/72 (81%)	66/79 (84%)	34/84 (41%)
	Yes	16/18 (89%)	11/12 (92%)	11/14 (79%)	10/13 (77%)
Smoking	No	30/34 (88%)	29/33 (88%)	31/37 (84%)	19/38 (50%)
	Yes	45/55 (82%)	40/51 (78%)	46/56 (82%)	25/59 (42%)
No. of Ulcers	1	64/74 (87%)	56/69 (81%)	67/82 (82%)	40/84 (48%)
	24	11/15 (73%)	13/15 (87%)	10/11 (91%)	4/13 (31%)

TABLE 4
Day and Night Pain Relief for the Treatment Groups at the End of Acute Phase
(Domestic Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

	Famotidine			
	40 mg/hs (89)	20 mg/bid (84)	40 mg/bid (93)	Placebo (97)
Day Pain				
No. of Patients with Pain Relief	86%*	78%*	80%*	53%
Median Time (days) to Pain Relief	11*	15*	9*	54
Night Pain				
No. of Patients with Pain Relief	87%*	77%*	91%*	56%
Median Time (days) to Pain Relief	10*	15*	6*	52

* Significantly different from placebo ($p < 0.001$)

TABLE 5
Antacid Consumption by Treatment Groups
(Domestic Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Treatment	(N)	Week 1	(N)	Week 2	(N)	Week 4	(N)	Week 8
Mean No. of Antacid Tablets								
40 mg/hs	(92)	1.7**	(87)	1.4**	(56)	1.0**	(21)	1.2
20 mg/bid	(84)	1.9	(80)	1.2**	(45)	1.0**	(18)	0.7**
40 mg/bid	(93)	1.5**	(84)	0.9**	(51)	0.6**	(12)	0.3*
Placebo	(98)	2.2	(95)	2.1	(70)	1.7	(37)	1.4
Mean Days of Antacid Therapy								
40 mg/hs	(92)	3.3	(87)	2.7**	(56)	2.2**	(21)	2.9
20 mg/bid	(84)	3.5	(80)	2.5**	(45)	1.9**	(18)	1.0**
40 mg/bid	(93)	2.9**	(84)	2.0**	(51)	1.3**	(12)	0.8**
Placebo	(98)	4.1	(95)	3.6	(70)	3.3	(37)	2.8

*,** Significantly different from placebo $p < 0.05$, $p < 0.01$

TABLE 6
Selected Characteristics of Treatment Groups at Baseline
(Domestic Duodenal Ulcer Study - Maintenance Phase)
Famotidine

Characteristic	40 mg/hs (54)	20 mg/hs (57)	Placebo (66)
Age (Years)			
Mean	51**	47	43
Sex			
Males	14 (26%)	15 (26%)	17 (26%)
Females	40 (74%)	42 (74%)	49 (74%)
Treatment During Acute Phase			
40 mg/hs	14 (26%)	18 (32%)	17 (26%)
20 mg/bid	16 (30%)	15 (26%)	12 (18%)
40 mg/bid	15 (28%)	16 (28%)	22 (33%)
Placebo	8 (17%)	7 (12%)	15 (23%)
Week During Which Ulcer Healed in Acute Study			
Week 2	29 (54%)[a]	26 (46%)	25 (38%)
Week 4	20 (37%)	20 (35%)	31 (47%)
Week 8	5 (9%)	11 (19%)	10 (15%)
Smoking			
Yes	31 (57%)[b]	40 (70%)	42 (64%)
No	23 (43%)	17 (30%)	24 (36%)
Drinking			
Yes	12 (22%)	8 (14%)	14 (21%)
No	42 (79%)	49 (86%)	52 (79%)
Initial Ulcer Size			
Mean (cm)	0.82	0.89	0.92

** Significantly different from placebo, $p < 0.01$
a,b different from placebo, p=0.08, p=0.10 respectively

TABLE 7
Duodenal Ulcer Relapse Rates by Treatment Groups
(Domestic Duodenal Ulcer Study - Maintenance Phase)
"Per Protocol"

Time		Famotidine 40 mg/hs	Famotidine 20 mg/hs	Placebo
Period 1 (Days 1-42)	No. Relapsed	0 (0%)	1 (2%)	8 (13%)
	No. Dropped out	8+	5+	11+
	Total number	49	49	62
	Cumulative Relapse Rate	0%**	2%*	13%
Period 2 (Days 43-105)	No. Relapsed	7 (17%)**	8 (19%)*	20 (47%)
	No. Dropped out	15+	8+	6+
	Total Number	41	43	43
	Cumulative Relapse Rate	17%**	20%**	53%
Period 3 (Days 106+)	No. Relapsed	3 (16%)[a]	2 (7%)**	6 (35%)
	No. Dropped out	16+	25+	11+
	Total Number	19	27	17
	Cumulative Relapse Rate	30%**	26%**	70%

*,** significantly different from placebo, $p < 0.05$, $p < 0.01$ respectively
a different from placebo, p=0.09
+ a large number of these patients had been in the maintenance phase for less than the required length of time and are still continuing in the study.

TABLE 8
Crude and Kaplan-Meier Estimated Cumulative Healing Rates
(International Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Treatment	Type of Estimate	N	Time of Endoscopy Week 4	Week 6	Week 8	End of Study
40 mg/hs	Crude	240	82 (34%)	164 (68%)	210 (87%)	211 (88%)
	Kaplan-Meier		34%	71%	92%	93%
	Dropouts		12	3	1	0
20 mg/bid	Crude	247	94 (38%)	191 (77%)*	228 (92%)	231 (93%)*
	Kaplan-Meier		38%	79%	95%	96%
	Dropouts		6	2	0	0
40 mg/bid	Crude	247	109 (44%)*	201(81%)*	227 (92%)	231 (93%)*
	Kaplan-Meier		44%	85%	97%	98%+
	Dropouts		12	1	0	0
150 mg/bid	Crude	246	96 (39%)	186 (76%)	222 (90%)	223 (91%)
	Kaplan-Meier		39%	77%	94%	94%
	Dropouts		7	3	2	0

* significantly better than 40 mg/hs, $p < 0.05$
+ significantly better than all other treatment groups, $p < 0.05$

TABLE 9
Day and Night Pain Relief for the Treatment Groups at the End of Acute Phase
(International Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

	Famotidine 40 mg/hs	Famotidine 20 mg/bid	Famotidine 40 mg/bid	Ranitidine 150 mg/bid
Day Pain				
No. of Patients with Pain Relief	81%	85%	81%	81%
Median Time (days) to Pain Relief	7.0	6.0	6.0	7.0
Night Pain				
No. of Patients with Pain Relief	85%	90%	88%	82%
Median Time (days) to Pain Relief	3.5	3.0**	3.0**	5.0

** significantly shorter than the ranitidine group, $p < 0.01$

TABLE 10
Antacid Therapy by Treatment Group
(International Duodenal Ulcer Study - Acute Phase)
"Per Protocol"

Mean Day of Antacid Therapy No. of Patients (%)	Week 1	Week 2	Week 4	Week 8
Famotidine				
40 mg/hs	2.0 100/241 (41%)	1.3 63/227 (28%)	0.8 22/132 (17%)	0.7 8/53 (15%)
20 mg/bid	1.6** 92/250 (37%)	0.9** 58/239 (24%)	1.0 24/140 (17%)	0.2 1/41 (2%)
40 mg/bid	1.7* 99/249 (40%)	1.1* 58/237 (24%)*	0.7 19/113 (17%)	0.5 2/28 (7%)
Ranitidine				
150 mg/bid	2.3 116/247 (47%)	1.6 81/237 (34%)	1.2 31/129 (22%)	0.7 5/40 (13%)

*,** significantly different from ranitidine group, $p < 0.05$, $p < 0.01$

TABLE 11
Cumulative Duodenal Ulcer Relapse Rates by Treatment Groups
(International Duodenal Ulcer Study - Maintenance Phase)
"Per Protocol"

Time		Famotidine 20 mg/hs	Placebo
Period 1 (Days 1-42)	No. Relapsed	5 (1.9%)**	39 (12.7%)
	No. Dropped out	26 (10.0%)+	33 (10.8%)++
	Total Number	268	306
	Cumulative Relapse Rate	1.9%**	12.7%
Period 2 (Days 43-105)	No. Relapsed	38 (16.0%)**	127 (54.3%)
	No. Dropped out	17 (7.2%)	12 (5.1%)
	Total Number	237	234
	Cumulative Relapse Rate	17.6%**	60.1%
Period 3 (Days 106 +)	No. Relapsed	27 (14.8%)**	31 (32.6%)
	No. Dropped out	2 (0.6%)	4 (4.3%)
	Total Number	182	95
	Cumulative Relapse Rate	29.8%**	73.1%

** significantly different from placebo, $p < 0.01$

TABLE 12
Distribution of Day and Night Pain
(International Duodenal Ulcer Study - Maintnance Phase)
"Per Protocol"

Score	Day Pain		Night Pain	
	Famotidine (N=259)	Placebo (N=301)	Famotidine (N=259)	Placebo (N=301)
Baseline				
None	211 (81%)	265 (88%)	228 (87%)	280 (93%)
Mild	45 (17%)	34 (11%)	27 (10%)	18 (6%)
Moderate	3 (2%)	2 (1%)	3 (2%)	3 (1%)
Severe	0	0	0	0
End of Study				
None	189 (73%)	109 (36%)	217 (84%)	154 (51%)
Mild	39 (15%)	64 (21%)	26 (10%)	49 (16%)
Moderate	27 (10%)	85 (28%)	12 (5%)	59 (20%)
Severe	4 (2%)	43 (15%)	4 (2%)	39 (13%)

TABLE 13
Cumulative Gastric Ulcer Healing Rates
(International Gastric Ulcer Study)
"Per Protocol"

Treatment		Week 4	Week 6	Week 8	End of Study
Famotidine 40 mg/hs (N=149)	No. Healed	70 (47%)**	97 (65%)**	120 (80%)**	120 (80%)**
	No. Dropped out	11	2	0	
	Kaplan-Meier L.T. Estimate	47%	68%	87%**	87%
Placebo (N=145)	No. Healed	45 (31%)	67 (46%)	78 (54%)	80 (55%)
	No. Dropped out	16	10	1	
	Kaplan-Meier L.T. Estimate	31%	49%	60%	62%

** Significantly greater than placebo, $p < 0.01$

TABLE 14
Salcita and Miwa's Six-Stage Classification
of Ulcer Healing

A_1 - Acute gastric ulcer with depth, exudate and edematous margins. No evidence of epithelial regeneration at the ulcer margin.

A_2 - Same as A_1 but with less edema. Evidence of epithelial regeneration can be seen at the ulcer margin.

H_1 - An ulcer remains but is 50 to 65% smaller than A_1 with regenerating epithelium extending into the ulcer base.

H_2 - Futher evidence of regeneration with an exudate 25 to 33% the diameter of A_1.

S_1 - Complete epithelialization with reddened background.

S_2 - Color of scar now indistinguishable from that of surrounding mucosa.

An ulcer was considered as healed if it was in either stage S_1 or S_2, and unhealed otherwise

TABLE 15
Cumulative Gastric Ulcer Healing Rates at Weeks 4 and 8
(Japanese Gastric Ulcer Study)
"Per Protocol"

Treatment		Week 4	Week 8	End of Study
Famotidine 20 mg/bid (N=96)	No. Healed	19 (26.4%)**	46 (63.9%)**	54 (75.0%)**
	No. Dropped out	5	1	1
	Kaplan-Meier LT Estimate	28.1%**	68.6%**	80.1%**
Gefernate 100 mg/tid (N=96)	No. Healed	3 (4.0%)	18 (24.0%)	23 (30.7%)
	No. Dropped out	19	2	0
	Kaplan-Meier LT Estimate	4.8%	32.5%	40.4%

** significantly greater than gefarnate, $p < 0.01$

Statistical Review and Evaluation
(Addendum)

NDA #: 19-462/Drug Class: 1C

Applicant: Merck, Sharp & Dohme Research Laboratories

Name of Drug: PEPCID (Famotidine) 40 mg/hs

Indication:

For treatment of active duodenal ulcers, gastric ulcers, the prophylactic use in duodenal ulcer disease, and the treatment of pathological hypersecretory conditions such as Zollinger-Ellison Syndrome.

Documents received:

Documents dated February 14, 1986, providing a breakdown of the ulcer relapse data in the U.S. and international duodenal ulcer maintenance studies by scheduled vs. unscheduled endoscopies based on the completed 12 month data, and one of two volumes dated March 4, 1986, providing arguments showing that gefarnate is superior to placebo.

A. On the Duodenal Ulcer Maintenance Studies

1. A Design Issue with Respect to the Prevention Claim

The principal hypothesis that was being tested in the duodenal prevention trials is that excessive nocturnal gastric acid secretion is the primary factor in the pathogenesis of duodenal ulcer. It was theorized that by inhibiting or controlling the amount of nocturnal gastric acid secretion with famotidine, one would induce an unfavorable condition for the normal development of duodenal ulcers. In the sponsor's trials, patients whose ulcers had just healed in an acute trial were randomized to either a famotidine or a placeoo arm. They were endoscoped at 3, 6, or 12 months or at unscheduled times at the discretion of the investigator if they reported symptoms suggestive of the presence of ulcers or for administrative reasons. Patients found to have an ulcer at any of these endoscopies were discontinued from the trial. The sponsor hoped to demonstrate ulcer prevention by showing that the cumulative proportion of patients with relapses at these prescheduled time points was significantly lower among the famotidine treated patients than among the placebo treated patients.

Under the sponsor's design, because scheduled endoscopies were relatively infrequent and far apart, an asymptomatic or mildly symptomatic ulcer may have recurred and rehealed before the next scheduled endoscopy and hence escaped detection. If an ulcer did recur, then it would be less likely to be observed under the famotidine treatment than under the placebo treatment because it has been demonstrated in the acute trials that famotidine relieved symptoms and healed ulcers faster than placebo (assuming, not unreasonably, that the maintenance dose of 20 mg/hs of famotidine is also a therapeutic dose). Therefore, in order to be able to make the prevention claim, one needs to be

able to estimate the amount of the observed treatment difference in the cumulative proportions of patients with relapses at the prescheduled times can actually be attributed to prevention. Since these trials did not provide the information needed for such estimates, one cannot draw at the present time an unambiguous inference with respect to ulcer prevention.

2. The Requirements for a Maintenance Claim

The content of this section reflects the conclusion reached in a recent discussion with Dr. Lipicky. Without sufficient information to be able to definitively conclude that famotidine prevented duodenal ulcer recurrence, a maintenance claim can still be made only if it can be demonstrated that maintenance therapy was beneficial to the patients with relatively low safety risk.

Within the context of the current design, a maintenance claim can be made for famotidine if these studies can successfully demonstrate a significant treatment difference in the observed proportions of both the unscheduled (mainly symptomatic) and the scheduled ulcer relapses in the first period. The rationale for these requirements is as follows:

Merely observing a significant treatment difference in the proportion of unscheduled (mainly symptomatic) relapses, but not in the scheduled relapses is not sufficient to establish a maintenance claim, because such result may be observed from a drug that simply relieves symptoms but does not accelerate healing and prevent recurrence. Thus, putting a patient on a maintenance therapy with such drug would be unwise because of the attendant risks involved in not treating an asymptomatic ulcer. On the other hand, merely observing a significant treatment difference in the proportion of scheduled relapses but not in the unscheduled relapses is not sufficient either, because such result may be anticipated of a drug that accelerates healing but does not relieve symptoms and prevent recurrence. For such drug, one should just treat the patient when an ulcer is detected and maintenance therapy should not be recommended. Whereas if both conditions were met, then a patient certainly would benefit from a maintenance treatment because he would experience a relief of symptoms and his ulcers would heal faster. It is sufficient to satisfy these requirements for the first period (0-3 months) because available evidence suggests that a preponderance of the observed relapses occurred early during the trial (51% of famotidine relapses and 71% of placebo relapses from U.S. Study and 45% of famotidine relapses and 78% of placebo relapses from the International Study occurred in the first period) and because dropping out these relapsers during the first period would make the treatment groups not quite comparable in the later periods (unless the first period was relatively short and not too many patients were dropped out, then the requirements may have to be satisfied for at least the first two periods. In any event, the results of the later periods can always be used as supportive evidence).

3. Study Results in Support of a Maintenance Claim

For the purpose of establishing the maintenance claim, only the two placebo-controlled maintenance studies 301 and 301C will be discussed here. The safety profile of famotidine has been discussed in the medical review by Dr. Bachrach.

The U.S. Study (see Table 1) demonstrated that famotidine patients had significantly lower proportion of unscheduled relapses (2.1% for famotidine 40 mg/hs and 1.1% for famotidine 20 mg/bid during the first 3 months than the placebo patients (20.5%, $p < 0.001$). Similarly, the famotidine patients also had a significantly lower proportion of scheduled relapses (9.4% for famotidine 40 mg/hs and 14.1% for famotidine 20 mg/bid) at 3 months than the placebo patients (28.6%, $p < 0.005$, $p < 0.05$). The same trend was observed for both the unscheduled and the scheduled relapses during the second period (4 - 6 months) with statistical significance achieved ($p < 0.05$) for the unscheduled relapses. The trend was evident in the third period but failed to reach statistical significance.

The International Study (see Table 2) demonstrated that during the first 3 months, famotidine patients had significantly fewer unscheduled relapses (4.4%) than placebo patients (21.8%, $p < 0.001$) and also significantly fewer scheduled relapses (13.0%) than placebo patients (51.3%, $p < 0.001$). The same trend was observed for the second period with statistical significance achieved at $p < 0.01$ and 0.03 for the unscheduled and scheduled, respectively. The same trend was also evident in the third period but failed to achieve significance at the 0.05 level.

Therefore, based on the results of these two placebo-controlled studies and the safety profile for famotidine, a maintenance claim can be recommended for famotidine 40 mg/hs in the long term treatment of duodenal ulcer disease.

B. <u>On the Gastric Ulcers</u>

1. Gefarnate is a marketed drug in Japan. Yet there is only one (presumably Japanese) trial comparing gefarnate to placebo. As shown in Table 3 provided by the sponsor, this trial failed to differentiate between gefarnate and placebo.

2. As pointed out by Dr. Lipicky at the Gastrointestinal Advisory Committee Meeting (January 16, 1986), a more appropriate and direct question is whether famotidine is superior to placebo in a U.S. population. The argument provided by the sponsor to show that famotidine is equivalent to either cimetidine or ranitidine is unsatisfactory. It was based on a comparison of different trial results across different countries. What is needed is at least a demonstration via a randomized trial of sufficient sample size that famotidine is equivalent to either cimetidine or ranitidine in a U.S population. However, in view of the higher placebo healing rate in the U.S., it would be wise to conduct instead a placebo controlled trial in the U.S.

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Concur: Dr. Dubey 4-15-86

Table 1
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Treatment	Ulcer Relapse	0-3 Months (0.3)	0-3 Months 3	3-6 Months (3, 6)	3-6 Months 6	6-12 Months (6, 12)	6-12 Months 12
Famotidine 40 mg/hs	Observed	2 (2.1%)	8 (9.4%)	2 (2.8%)	8 (11.8%)	1 (2.6%)	2 (6.3%)
	Not observed	95	77	70	60	38	30
	Not Evaluable	9	10*	4	2*	5	2*
	Total	106	95	76	70	44	34
Famotidine 20 mg/bid	Observed	1 (1.1%)	11 (14.1%)	1 (1.4%)	3 (4.5%)	1 (2.2%)	3 (7.0%)
	Not observed	89	67	70	64	44	40
	Not Evaluable	7	11*	1	3*	6	0*
	Total	97	89	72	70	51	43
Placebo	Observed	18 (20.5%)	18 (28.6%)	6 (13.6%)	4 (11.7%)	3 (13.6%)	2 (10.5%)
	Not observed	70	45	38	30	19	17
	Not Evaluable	11	7*	1	3*	1	0*
	Total	99	70	45	37	23	19
wo-sided p-value	40 mg/hs vs. Placebo	p<0.001	p<0.005	p<0.05	p<0.10	p<0.10	p<0.10
ni-square test	20 mg/bid vs. Placebo	p<0.001	p<0.05	p<0.01	p<0.10	p<0.10	p<0.10

Including patients who did not have scheduled endoscopies

Table 2
International Duodenal Ulcer Maintenance Study

Treatment	Ulcer Relapse	0-3 Months (0.3)	0-3 Months 3	3-6 Months (3, 6)	3-6 Months 6	6-12 Months (6, 12)	6-12 Months 12
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$x^2 = 1.84$
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Two-sided p-value Chi-square test	40 mg/hs vs. Placebo	p<0.001	p<0.005	p<0.05	p<0.10	p<0.10	p<0.10
	20 mg/bid vs. Placebo	p<0.001	p<0.05	p<0.01	p<0.10	p<0.10	p<0.10

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$x^2 = 1.84$
$p>0.15$

Outpatients with endoscopically confirmed healed ulcers

	PEPCID 40 mg h.s. (N = 89)	PEPCID 20 mg b.i.d. (N = 84)	Placebo h.s. (N = 97)
Week 2	*32%	*38%	17%
Week 4	*70%	*67%	31%

*Statistically significantly different than placebo ($p < 0.001$)

Patients not healed by week 4 were continued in the study. By week 8, 83% of patients treated with PEPCID had healed versus 45% of patients treated with placebo. The incidence of ulcer healing with PEPCID was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients receiving PEPCID than for patients receiving placebo; patients receiving PEPCID also took less antacid than the patients receiving placebo.

Long-Term Maintenance
Treatment of Duodenal Ulcers

PEPCID, 20 mg p.o. h.s. was compared to placebo h.s. as maintenance therapy in two double-blind, multicenter studies of patients with endoscopically confirmed healed duodenal ulcers. In the U.S. study the observed ulcer incidence within 12 months in patients treated with placebo was 2.4 times greater than in the patients treated with PEPCID. The 89 patients treated with PEPCID had a cumulative observed ulcer incidence of 23.4% compared to an observed ulcer incidence of 56.6% in the 97 patients receiving placebo ($p<0.01$). These results were confirmed in an international study where the cumulative observed ulcer incidence within 12 months in the 307 patients treated with PEPCID was 35.7%, compared to an incidence of 75.5% in the 325 patients treated with placebo ($p<0.01$).

Gastric Ulcer

In both a U.S. and an international multicenter, double-blind study in patients with endoscopically confirmed active benign gastric ulcer, orally administered PEPCID, 40 mg h.s., was compared to placebo h.s. Antacids were permitted during the studies, but consumption was not significantly different between the PEPCID and placebo groups. As shown in the table below, the incidence of ulcer healing (dropouts counted as unhealed) with PEPCID was statistically significantly better than placebo at weeks 6 and 8 in the U.S. study, and at weeks 4, 6 and 8 in the international study, based on the number of ulcers that healed, confirmed by endoscopy.

Patients with endoscopically confirmed healed ulcers

	U.S. Study		International Study	
	PEPCID 40 mg h.s. (N = 74)	Placebo h.s. (N = 75)	PEPCID 40 mg h.s. (N = 149)	Placebo h.s. (N = 146)
Week 4	45%	39%	**47%	31%
Week 6	**68%	44%	**65%	46%
Week 8	*78%	64%	**80%	54%

*,**Statistically significantly better than placebo ($p \leq 0.05$, $p \leq 0.01$ respectively)

Time to complete relief of daytime and nighttime pain was statistically significantly shorter for patients receiving PEPCID than for patients receiving placebo; however, in neither study was there a statistically significant difference in the proportion of patients whose pain was relieved by the end of the study (week 8).

Pathological Hypersecretory Conditions
(e.g., Zollinger-Ellison Syndrome
Multiple Endocrine Adenomas)

In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome with or without multiple endocrine adenomas, PEPCID significantly inhibited gastric acid secretion and controlled associated symptoms. Doses from 20 to 160 mg q 6 h maintained basal acid secretion below 10 mEq/hr; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. PEPCID was well tolerated at these high dose levels for prolonged periods (greater than 12 months) in eight patients, and there were no cases reported of gynecomastia, increased prolactin levels, or impotence.

Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension, MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

INDICATIONS AND USAGE

PEPCID is indicated in:

1. *Short term treatment of active duodenal ulcer.* Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.

2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies have not extended beyond one year.

3. *Short term treatment of active benign gastric ulcer.* Most patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

4. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas).*

PEPCID I.V. is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or as an alternative to the oral dosage forms for short-term use in patients who are unable to take oral medication.

CONTRAINDICATIONS

Hypersensitivity to any component of these products.

PRECAUTIONS

General

Symptomatic response to therapy with PEPCID does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency

Longer intervals between doses or lower doses may need to be used in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.) However, currently, no drug-related toxicity has been found with high plasma concentrations of famotidine.

Information for Patients

The patient should be instructed to shake the oral suspension vigorously for 5 - 10 seconds prior to each use. Unused constituted oral suspension should be discarded after 30 days.

Drug Interactions

No drug interactions have been identified. Studies with famotidine in man, in animal models, and *in vitro* have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

Carcinogenesis, Mutagenesis,
Impairment of Fertility

In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for PEPCID.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate. In *in vivo* studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day fertility and reproductive performance were not affected.

Pregnancy
Pregnancy Category B

Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day respectively and in both species at I.V. doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to PEPCID. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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Nursing Mothers

Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 600 times the usual human dose. It is not known whether this drug is secreted into human milk. Because many drugs are secreted into human milk and because of the potential for serious adverse reactions in nursing infants from PEPCID, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). Dosage adjustment in the case of severe renal impairment may be necessary.

ADVERSE REACTIONS

The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In those controlled clinical trials in which PEPCID Tablets were compared to placebo, the incidence of adverse experiences in the group which received PEPCID Tablets, 40 mg at bedtime, was similar to that in the placebo group.

The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

The following other adverse reactions have been reported in clinical trials. While a causal relationship could not be established for these infrequently reported events, causality cannot be excluded.

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: palpitations

Gastrointestinal: nausea, vomiting, abdominal discomfort, anorexia, dry mouth, liver enzyme abnormalities

Hematologic: thrombocytopenia

Hypersensitivity: orbital edema, conjunctival injection

Musculoskeletal: musculoskeletal pain, arthralgia

Nervous System/Psychiatric: paresthesia; grand mal seizure (single report); psychic disturbances including depression, anxiety, decreased libido, hallucinations (single report); insomnia; somnolence

Respiratory: bronchospasm

Skin: alopecia, acne, pruritus, dry skin, flushing

Special Senses: tinnitus, taste disorder

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V. In addition, transient irritation at the injection site has been observed with PEPCID I.V.

OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD_{50} of famotidine in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 2000 mg/kg. Famotidine did not produce overt effects at high oral doses in mice, rats, cats and dogs, but induced significant anorexia and growth depression in rabbits starting with 200 mg/kg/day orally. The intravenous LD_{50} of famotidine for mice and rats ranged from 254-563 mg/kg and the minimum lethal single I.V. dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in I.V. treated dogs were emesis, restlessness, pallor of mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended oral dose is 20 mg once a day at bedtime.

Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension, MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

Benign Gastric Ulcer

Acute Therapy: The recommended adult oral dosage for active benign gastric ulcer is 40 mg once a day at bedtime.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)

The dosage of PEPCID in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q 6 h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q 6 h have been administered to some patients with severe Zollinger-Ellison Syndrome.

Oral Suspension

PEPCID Oral Suspension may be substituted for PEPCID Tablets in any of the above indications for those patients who cannot swallow tablets. Each five mL contains 40 mg of famotidine after constitution of the powder with 46 mL of Purified Water as directed.

Directions for Preparing PEPCID Oral Suspension

Prepare suspension at time of dispensing. Slowly add 46 mL of Purified Water. Shake vigorously for 5 - 10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension

Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration

In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, PEPCID I.V. may be administered. The recommended dosage is 20 mg q 12 h.

Preparation of PEPCID Intravenous Solutions

Dilute 2 mL of PEPCID I.V. (solution containing 10 mg/mL) with 0.9% Sodium Chloride Injection or other compatible intravenous solution to a total volume of either 5 mL or 10 mL and inject over a period of not less than 2 minutes.

Preparation of PEPCID Intravenous Infusion Solutions

PEPCID I.V. may also be administered as an infusion, 2 mL diluted with 100 mL of 5% dextrose or other compatible solution, and infused over a 15-30 minute period.

Stability of PEPCID I.V.

PEPCID I.V. is stable for 48 hours at room temperature when added to or diluted with most commonly used intravenous solutions, e.g., Water for Injection, 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, Lactated Ringer's Injection, or Sodium Bicarbonate Injection, 5%.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency

In patients with severe renal insufficiency, i.e., with a creatinine clearance less than 10 mL/min, the elimination half-life of PEPCID may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dose of PEPCID may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

HOW SUPPLIED

No. 3535 — Tablets PEPCID, 20 mg, are beige colored, U-shaped, film-coated tablets coded MSD 963. They are supplied as follows:

NDC 0006-0963-31 unit of use bottles of 30
NDC 0006-0963-28 unit dose package of 100.

No. 3536 — Tablets PEPCID 40 mg, are light brownish-orange, U-shaped, film-coated tablets coded MSD 964. They are supplied as follows:

7146306

[redacted] PEPCID® (Famotidine, MSD)
[redacted] Oral Suspension PEPCID®
[redacted] for Oral Suspension, MSD)
[redacted] PEPCID® I.V. (Famotidine, MSD)
[redacted]
NDC 0006-0[redacted] unit of use bottles of 30
(6505-01-257-3184, 40 mg 30's)
NDC 0006-0854-28 unit dose package of 100.

No. 3638 — Oral Suspension PEPCID is a white to off-white powder containing 400 mg of famotidine for constitution. When constituted as directed, PEPCID Oral Suspension is a smooth mobile, off-white, homogenous suspension with a cherry-banana-mint flavor, containing 40 mg of famotidine per 5 mL.

NDC 0006-3638-92, bottles containing 400 mg famotidine.

FOR INTRAVENOUS USE ONLY

No. 3639 — Injection PEPCID I.V. 10 mg per 1 mL, is a non-preserved, clear, colorless solution and is supplied as follows:

NDC 0006-3639-04, 10 x 2 mL single dose vials.

Tablets PEPCID® (Famotidine, MSD)
Oral Suspension PEPCID®
(Famotidine for Oral Suspension MSD)
Injection PEPCID® I.V. (Famotidine, MSD)

No. 3641—Injection PEPCID I.V. 10 mg per 1 mL, is a clear, colorless solution and is supplied as follows:

NDC 0006-3541-14, 4 mL vials.

Storage

Avoid storage of PEPCID Tablets at temperatures above 40°C (104°F).

Avoid storage of the powder for oral suspension at temperatures above 40°C (104°F). After constitution store the suspension below 30°C (86°F). Do not freeze. Discard unused suspension after 30 days.

Store PEPCID I.V. at 2-8°C (35.6-46.4°F). If solution freezes, bring to room temperature; allow sufficient time to solubilize all the components.

When diluted as recommended (see DOSAGE AND ADMINISTRATION) PEPCID I.V. is stable for 48 hours at room temperature.

MSD MERCK SHARP & DOHME
DIV OF MERCK & CO., INC. WEST POINT, PA [redacted] USA

Issued September 1988

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Printed in USA

Statistical Review and Evaluation

Date: JUL 29 1988

NDA# 19-462/S-003

Applicant: Merck, Sharp & Dohme Research Laboratories

Name of Drug: PEPCID (Famotidine) 40 mg H.S.

Indication: For short-term treatment of active benign gastric ulcer

Documents Reviewed: Supplement Vol. 2.1, 2.6 - 2.10 (plus statistical addenda dated 11/16/87, 12/10/87 and 3/10/88)

I have discussed this review with Stephen Fredd, M.D. and Hugo Gallo-Torres, M.D. (HFD-180) and Drs. Fredd and Gallo-Torres agreed with my findings.

A. Background

Famotidine was recently approved and used in the United States for the treatment of active duodenal ulcer. In the NDA supplement under review, the sponsor seeks approval for a claim of efficacy in the treatment of acute benign gastric ulcer.

The sponsor has submitted three controlled clinical studies in support of this proposed claim. The first and second are randomized double-blind multicenter studies conducted in the United States. The first compared famotidine 40 mg H.S. to placebo and the second compared famotidine 40 mg H.S. to ranitidine 150 mg B.I.D. The third is a randomized double-blind multi-country study conducted in foreign countries which compared famotidine 40 mg H.S. to placebo. This international trial submitted as part of the original NDA of June 24, 1985 for famotidine tablets has been reviewed by Dr. Chi and was documented in "Statistical Review and Evaluation dated April 14, 1986."

Since similar design and methods of analysis were used in all three studies, they will be described in detail only in the first study.

B. Domestic Placebo-Controlled Study

1. Description of Study

This was a multicenter (10), double blind, randomized, placebo-controlled trial comparing the effects of famotidine 40 mg H.S. with placebo in the short-term treatment of acute benign gastric ulcer. The objective of the study is to determine the efficacy of

famotidine 40 mg H.S. in the short-term treatment of active gastric ulcer.

During the initial screening visit, a complete physical and laboratory examination were performed and pertinent baseline information (e.g. alcohol, smoking, caffeine consumption, etc) were obtained. An endoscopy was performed at this time to verify the presence of a gastric ulcer and to determine the number, size, and location of the ulcer(s). The presence of gastritis was also noted. The patients selected for this study had a primary diagnosis of acute gastric ulcer confirmed by endoscopy and proved benign by multiple biopsies and cytology. Patients with a 0.5 to 2.5 cm ulcer who exhibited clinical symptoms of active gastric ulcer and met admission criteria were permitted to enter the study.

The patients were randomly assigned to either famotidine 40 mg H.S. or placebo. The randomization was stratified by investigator and by ulcer size (<=1 cm and >1 cm in diameter). Clinical symptoms were assessed at weeks 2, 4, 6, and 8. Endoscopy was performed at weeks 4, 6, and 8. Ulcer healing was defined as complete epithelialization of the ulcer crater. Patients whose endoscopy revealed all ulcers healed at any visit were considered to have completed the study. In addition, severity of daytime and nighttime pain was recorded at baseline. Patients were instructed to rate daytime/nighttime pain on 4-point severity scale: 0=none, 1=mild, 2=moderate, 3=severe and to record the rating in a diary daily for eight weeks. Patient's daily pain scores for days 1 to 7 and weekly pain evaluation for weeks 2 to 8 were recorded by investigator on the case report form.

During the treatment period, patients were instructed to avoid caffeine, alcohol and smoking. Gelusil antacid tablets was dispensed to patients by investigator. Patients were permitted to take two tablets PRN for pain but not until at least one hour after coded medication. The number of antacid tablets consumed was recorded in the diary on a daily basis.

Primary measure of efficacy was the cumulative ulcer healing rate at weeks 4, 6 and 8. Secondary measures of efficacy were the severity of daytime and nighttime pain and antacid consumption. Pain was assessed on a daily basis by the patient and recorded on the patient diary.

2. Sponsor's Study Results

A total of 157 patients representing 10 investigators were entered into the study and were randomized to two treatment groups. These treatment groups were generally comparable at baseline with respect to various pertinent patient characteristics such as age, sex, smoking, drinking, ulcer size etc. During this trial, 8 patients violated protocol. Of the

remaining 149 patients, 10 were discontinued due to adverse experience, ineffective therapy or other reasons.

Efficacy analysis was done on two data sets: the "per protocol" and the "all patients treated" data sets. The former excluded all patients who were protocol violators and the latter included all randomized patients who had baseline and some post-baseline treatment values. The results based on these two data sets are similar. Only results based on the "per protocol" data set will be discussed below except for antacid consumption.

The primary efficacy measure was the cumulative frequencies of healed ulcers observed via endoscopy at weeks 4, 6, and 8. The healing rates were compared between the two treatment groups using Fisher's Exact test (see Table 1). In this analysis, dropouts were considered as not healed. The sponsor's reported p-values are given in Table 1. The Fisher's Exact test shows that the famotidine group had significantly higher cumulative healing rates than the placebo group only at 6 weeks ($p = 0.008$) but not at weeks 4, 8 and after week 8. The sponsor also obtained the Kaplan-Meier life table estimate of the cumulative healing rates which are also presented in Table 1. This method assumed that dropouts healed at the same rate as those observed for patients who completed the study. In the life table analysis, the famotidine group was only marginally significantly better than placebo ($p = 0.048$).

The relationship between the various concomitant factors (initial ulcer size, smoking, drinking, antacid use, esophagus condition, and caffeine) and ulcer healing after week 8 were given in Table 2 and were assessed using the Mantel-Haenszel method. The results indicated that none of these factors had a statistically significant ($p<=0.05$) relationship to ulcer healing. Further analysis indicated that the observed differences in healing rates between the famotidine and placebo groups were maintained after adjusting for these factors. However it is of interest to point out that for this study, the effect of famotidine appears to be more pronounced in patients with larger ulcers. The effect of famotidine appears to be attenuated by either smoking or use of caffeine. Famotidine also appears to be more effective in patients with abnormal esophagus conditions.

The secondary efficacy measures included the severity of daytime and nighttime pain and antacid consumption. Daytime and nighttime pains were assessed by time to relief of pain using the Mantel-Haenszel method stratifying for baseline pain score. The results for the "per protocol" data as shown in Table 3 indicated that although no significant difference was observed in terms of the proportion of patients with pain relief, the famotidine patients experienced significantly faster pain relief than the placebo patients in terms of the time to pain relief ($p <= 0.05$).

Antacid consumption was assessed by comparing the proportion of "all patients treated" in each group who took antacid therapy at any time during the study and by comparing the mean number of tablets taken daily and the mean number of days of antacid therapy during weeks 1, 4, 6, and 8. Fisher's Exact Test was used to analyze the difference in the proportion of patients receiving antacid therapy between treatment groups. The Kruskal-Wallis Test was used to analyze the difference in the number of days of antacid therapy between treatment groups. The results based on "all patients treated" data set are displayed in Table 4. No significant differences between the two treatment groups were observed.

3. Reviewer's Evaluation

The cumulative healing rate was also analyzed by this reviewer using the Fisher's Exact test and the Mantel-Haenszel method. The Fisher's Exact test produced p-values that are larger (less significant) than those reported by the sponsor, where the Mantel-Haenszel statistic produced p-values that are similar to the sponsor's reported results (see Table 1). These results essentially show that there are no significant treatment effect other than at week 6.

This reviewer has also analyzed the healing rate data adjusted for the time-of-endoscopy. In this analysis, the Cochran-Mantel-Haenszel statistic was computed based on the per protocol data set with dropouts being considered as not healed. The results displayed in Table 5 show that there is a significant overall treatment effect (p=0.031). However, there is also a significant treatment by time-of-endoscopy interaction (p=0.03); that is, the treatment effect was not consistent across the different time periods. It is apparent that the significant overall treatment effect essentially reflects the significant treatment effect during weeks 4-6 (p=0.001) which is essentially a consequence of the extremely low placebo healing rate during this period. As seen in Table 5, the placebo healing rate during this period (weeks 4-6) of 9% is very low compared to the placebo healing rates during either weeks 0-4 or weeks 6-8 (39% and 36% respectively) and also low when compared to the placebo healing rates of 35%, 30% and 22% during weeks 0-4, weeks 4-6 and weeks 6-8 respectively in the international placebo-controlled study (see Table 6).

In this study, because the placebo group had more dropouts than the famotidine group (16% vs 8%), the healing rates were also compared based on an "equal probability imputation" analysis where half of the dropouts were handled as healed in both famotidine and placebo groups. The results of the Cochran-Mantel-Haenszel statistic based on this analysis is given in Table 7 which shows that there is no overall significant treatment effect (p=0.103) and that there is still a significant treatment by time-of-endoscopy interaction (p=0.04) reflecting again the very

low placebo healing rate observed during weeks 4-6. Similar results are obtained in an evaluable patients analysis where all dropouts were excluded from the per protocol analysis (see Table 8).

The relationship between antacid consumption and cumulative ulcer healing was also examined by this reviewer. The maximum number of antacid tablets allowed per day was not specified in the protocol. The sponsor provided the "average daily antacid consumption" data upon this reviewer's request. Average daily antacid consumption was defined as a ratio of the total number of tablets the patient took during the study to the number of days he/she was in the study. Table 9 displays the results of "per protocol" analysis of the number of patients healed or not healed by week and treatment controlling for average daily antacid consumption. As seen from Table 9, the differences in healing rates between treatment groups are statistically significant at week 6 and nonsignificant at week 4, week 8 and after week 8. Furthermore, statistically significant advantage of famotidine over placebo at week 6 occurred only for patients with 3 or more average daily antacid consumption (see Table 9). There was a hint of an advantage of famotidine over placebo for patients with 3 or more average daily antacid consumption at week 8 and after week 8 ($p=0.109$). This suggests that perhaps multiple doses of concomitant antacid therapy may enhance the rate of ulcer healing particularly for famotidine treated patients.

C. Domestic Ranitidine Control Study

1. Description of Study

The objective of this study was to compare the clinical efficacy and safety of famotidine 40 mg H.S. to ranitidine 150 mg B.I.D. in the short term treatment of acute gastric ulcer. The study design was similar to the preceding domestic placebo control study except with ranitidine in place of placebo. The approach and the methods of analysis were generally the same as those employed in the preceding study.

2. Sponsor's Study Results

A total of 195 patients representing 15 investigators were entered into the study and were randomized to two treatment groups (96 famotidine group and 99 ranitidine group). These treatment groups were generally similar with respect to various baseline patient characteristics (e.g. smoking, drinking etc.) except for location of ulcer and other conditions in the esophagus (see Table 10).

During this trial, 26 patients violated protocol. Of the remaining 169 patients, 19 were discontinued due to adverse experience, ineffective therapy and other reasons. The protocol violators were excluded from the "per protocol" efficacy

analysis. The crude healing rate was assessed using the Fisher's Exact test. Dropouts were considered to be not healed. The crude and Kaplan-Meier life table estimate of the cumulative healing rates are shown in Table 11. There was no statistically significant difference between treatment groups at any time period with respect to either the crude or life table estimate of the ulcer healing rates.

The relationship between the various concomitant factors and ulcer healing was assessed after 8 weeks of therapy. Stratification of the analysis by each of these factors had no effect on the comparisons of treatments with respect to the proportion of patients healed (see Table 12). The time to healing data were analyzed in the life table analysis including the factors in the statistical model. The model contained treatment, concomitant factor(s) and treatment by factor interactions. No statistically significant difference were observed between treatment groups. However it would be of interest to point out that for this study the healing rates were higher among caffeine consumer than among non-caffeine consumer and higher among patients with moderate daytime/nighttime pain than patients with mild daytime/nighttime pain. The association of factor to healing rate was similar for the two treatment groups for most of the factors except age. This was due to the fact that the famotidine group had a higher healing rate for patients over 60 and the ranitidine group had a higher healing rate in patients between 40 and 59. The relationship of various factors to proportion of patients with ulcer healing and time to healing was also assessed. The factors with a statistically significant ($p<=0.05$) relationship to ulcer healing are given in Table 13.

There was no significant difference between treatments with respect to the proportion of patients with pain relief and time to pain relief. The results based on "per protocol" analysis are displayed in Table 14. The use of antacid therapy was assessed. The results are summarized in Table 15. No significant difference between the two groups was observed.

3. Reviewer's Evaluation

The sample size needed to detect a 15% difference for ulcer healing after 8 weeks of therapy between treatment groups with 5% level of significance and 80% power assuming that the estimation of the famotidine healing rate after 8 weeks is 90% had been determined in the sponsor's study protocol. The study protocol called for a sample size of 100 patients per group. The sample size is found too low compared to 113 patients per group obtained using an improved approximation method given in "Fleiss (1981) Statistical Methods for Rates and Proportions, pages 33 - 49". With 169 patients completed the study (82 for famotidine 40 mg H.S. and 87 for ranitidine 150 mg B.I.D.), the power would be at most 75%. This would mean a greater chance of not being able to

detect a significant difference between treatments, if a difference does exist. Furthermore, the 15% difference from active control may not be clinically meaningful, because as one can see from the domestic placebo-controlled study (Table 1), the difference between famotidine and placebo already falls within this range and such sample size is not even sufficient to distinguish famotidine from placebo let alone an active control.

C. International Placebo-Controlled Study

1. Description of Study

The primary objective of this study was to determine the efficacy and safety of famotidine 40 mg H.S. in the short term treatment of acute gastric ulcer. This was an 8-week double-blind, randomized, multicenter (44 investigators across 14 countries) and placebo-controlled study. Patients with primary diagnosis of active gastric ulcer between 0.5 to 2.5 cm confirmed by endoscopy were eligible to enter the study subject to some other entry criteria. Assessments of clinical symptoms and endoscopies were performed at week 0 (baseline) and weeks 4, 6 and 8. Patients whose ulcers had completely healed by the time of any visit were considered to have completed the study. Patients whose ulcer had not healed at the end of eight weeks of therapy were considered to have completed the study as treatment failures. Patients were instructed to record daily evaluations of day and night pain, antacid consumption and any adverse experience. Concomitant therapies, antacid consumption and dosage of test drug taken during the study were recorded by the investigator at each visit.

2. Sponsor's Study Results

A total of 336 patients entered the study. One hundred sixty-seven patients were assigned to the famotidine 40 mg HS treatment and 169 the placebo treatment. Both treatment groups were comparable at baseline with respect to various pertinent baseline characteristics except for drinking habits. A higher proportion of patients in the placebo group were regular alcohol users than patients in the famotidine group (59% versus 42%, $p<0.01$).

The observed healing rate was assessed using the Fisher's Exact test. Dropouts were considered to be not healed. The crude cumulative healing rates were significantly ($p< 0.01$) greater for the famotidine group than for the placebo group at weeks 4, 6 and 8 (47% versus 31% at week 4, 65% versus 46% at week 6 and 80% versus 54% see Table 15). At week 8 the Kaplan-Meier life table estimates of the healing rate was significantly greater for the famotidine group than for the placebo group (87% versus 60%, $p<0.01$).

The data suggested significant relationship between ulcer healing

and initial ulcer size and antacid use. However, no significant treatment by factor and treatment by investigator interactions were found; the treatment differences were generally consistent across investigators and various factor.

The two treatment groups were similar at baseline with respect to day pain and night pain, with over 73% and 48% of patients having moderate or severe pain respectively. Patient from both treatment groups experienced significant pain relief starting at day 1 ($p<0.01$) and continue to the end of the study. The famotidine group had a significantly shorter median time to day pain relief (14 days versus 35 days, $p<0.01$). No significant treatment differences were observed in the relief of night pain. There were significant differences between the treatment groups at Days 2, 4, 5, 6, and 7 in the proportion of patients taking antacid therapy ($p<0.05$).

3. Reviewer's Evaluation

The healing data was also analyzed by this reviewer using the Mantel-Haenszel method. The result is the same as the sponsor's finding.

In this clinical trial, because the placebo group had more dropouts than the famotidine group (19% versus 9%), the crude healing rates comparison would tend to be more favorable to the famotidine group. In order to assess the possible effect of the "dropout", This reviewer conducted an "equal probability imputation" analysis in which half of the dropouts were handled as healed in both famotidine and placebo groups. In this analysis, significant difference was shown at each time period (see Table 17). This result is similar to the result obtained in the "evaluable patients" analysis based on evaluable patients who were not protocol violators (see Table 17). Famotidine was superior to placebo at weeks 4, 6 and 8 in healing rates.

D. Overall Summary and Recommendation

The domestic ranitidine control study does not provide much information because the 15% difference in healing rates to be detected is too large. As the domestic placebo control study shows, the observed difference in healing rates between famotidine and placebo is only 13%. Furthermore, the available sample size only has a power of 75% to detect the 15% difference.

The international placebo control study demonstrated that famotidine is significantly more effective than placebo ($p<0.01$).

In the domestic placebo control study, even though the Cochran-Mantel-Haenszel statistic shows a significant overall treatment effect ($p=0.031$), it also demonstrates a significant treatment by

time-of-endoscopy interaction; that is, the treatment effect was not consistent across the time periods. This basically reflects a significant treatment effect observed only during 4-6 weeks period as a result of an unusually low placebo healing rate (9%) during this period. This placebo healing rate is low when compared to the placebo healing rates of 39% and 36% during weeks 0-4 and 6-8 respectively in the same study and to the placebo healing rates of 35%, 30% and 22% during weeks 0-4, 4-6, and 6-8 respectively in the international placebo control study. The latter comparison is particularly puzzling because the placebo healing rate in the European patient population is usually lower.

Thus, the overall significant treatment effect observed in the domestic placebo control study would probably be nonexistent if it were not for the unusually low placebo healing rate observed for 4-6 weeks period. For example, an equal probability imputation analysis (Table 7) and an evaluable patients analysis (Table 8) both show that the overall significance level (p=0.103 and p=0.07 respectively) of the treatment effect is very sensitive to the placebo healing rates. Furthermore, in both analyses, there were still significant treatment by time-of-endoscopy interaction (p=0.04 and p=0.13 respectively). Consequently, the evidence presented from the domestic placebo control study is not persuasive.

E. Comments to be Conveyed to the Sponsor

The contents of Section D may be conveyed to the sponsor.

Milton C. Fan
Milton C. Fan, Ph.d
Mathematical Statistician

This review consists of 9 pages of text and 16 pages of tables.

concur: Dr. Chi Chi 7/29/88

Dr. Dubey 7-29-88

cc: Orig. NDA 19-462
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Gallo-Torres
HFD-344/DR. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2. NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Fan
Chron.
Dr. Fan/x30263/mcf/7/28/88

Table 1
Cumulative Healing Rates and Kaplan-Meier Estimated Cumulative Healing Rates

(Domestic Placebo-Controlled Study)

"Per Protocol"

Time of Endoscopy

Treatment	Type of Estimate	N	Week 4 Healing Rates	Week 4 sponsor's reported p-value	Week 4 Fisher's Exact p-value	Week 4 M-H Chi-squar p-value	Week 6 Healing Rates	Week 6 sponsor's reported p-value	Week 6 Fisher's Exact p-value	Week 6 M-H Chi-square p-value
Famotidine 40 mg H.S.	Crude	74	33 (45%)	n.s.	0.508	0.464	49 (66%)	<=0.01	0.008	0.007
	Kaplan-Meier		45%				70%			
	dropouts		6				0			
Placebo	Crude	75	29 (39%)				33 (44%)			
	Kaplan-Meier		39%				46%			
	dropouts		10				1			

Time of Endoscopy

Treatment	Type of Estimate	N	Week 8 Healing Rates	Week 8 sponsor's reported p-value	Week 8 Fisher's Exact p-value	Week 8 M-H Chi-squar p-value	After week 8 Healing Rates	After week 8 sponsor's reported p-value	After week 8 Fisher's Exact p-value	After week 8 M-H Chi-square p-value
Famotidine 40 ag H.S.	Crude	74	58 (78%)	<=0.05	0.070	0.054				
							59 (80%)	n.s.	0.096	0.073
	Kaplan-Meier		84%							
							86%			
	dropouts		9							
							9			
Placebo	Crude	75	48 (64%)							
							50 (67%)			
	Kaplan-Meier		72%							
							76%			
	dropouts		1							

2-tail Fisher's exact test and Mantel-Haenszel chi-square p-values were obtained by reviewer for comparisons to placebo for healing rates

=0.048 was obtained by the sponsor for the life table analysis

Table 2

Frequency and Percent of Patients with Ulcer Healed After Week 8 Stratified by Selected Factors

(Domestic Placebo-Controlled Study)

"Per Protocol"

Factor	Level	Famotidine 40 mg H.S.	Placebo
Ulcer size (cm)	0.5-0.95	35/43 (81%)	26/35 (74%)
	1.00-1.45	13/16 (81%)	15/23 (65%)
	1.50-	11/15 (73%)	9/17 (53%)
Smoking	No	25/31 (81%)	23/37 (62%)
	Yes	34/43 (79%)	27/38 (71%)
Drinking	No	56/69 (81%)	43/67 (64%)
	Yes	3/5 (60%)	7/8 (88%)
Antacid use	No	4/6 (67%)	4/9 (44%)
	Yes	55/68 (81%)	46/66 (70%)
Esophagus conditions	No	46/60 (77%)	41/61 (67%)
	Yes	13/14 (93%)	9/14 (64%)
Duodenal conditions	No	51/63 (81%)	42/63 (67%)
	Yes	8/11 (73%)	8/12 (67%)
Age group	under 40	9/11 (82%)	8/13 (62%)
	40-59	27/35 (77%)	24/34 (71%)
	60 or over	23/28 (82%)	18/28 (64%)
Caffeine	No	16/17 (94%)	11/20 (55%)
	Yes	43/57 (75%)	39/55 (71%)
No. of ulcers	single	49/62 (79%)	44/65 (68%)
	multiple	10/12 (83%)	6/10 (60%)

Table 3
Daytime and Nighttime Pain Relief for the Treatment Groups at the End of Study

(Domestic Placebo-Controlled Study)

"Per Protocol"

	Famotidine 40 mg H.S	Placebo
Daytime pain		
No. of patients without pain	44/69 (64%)	41/68 (60%)
Median time (days) to pain relief	28*	54
Nighttime pain		
No. of patients without pain	44/64 (69%)	43/66 (65%)
Median time (days) to pain relief	25*	48

* significantly different from placebo ($p<=0.05$)

Table 4
Antacid Consumption by Treatment Groups

(Domestic Placebo-Controlled Study)

"All Patients Treated"

Statistics	Treatment	(N)	Week 1	(N)	Week 4	(N)	Week 6	(N)	Week 8
Mean No. of Antacid Tablets	Famotidine 40 mg H.S.	70	3.36	65	2.35	32	2.02	15	1.57
	Placebo	67	3.61	62	2.59	33	2.42	25	1.90
Mean Days of Antacid Therapy	Famotidine 40 mg H.S.	70	5.2	65	3.5	32	3.2	15	3.0
	Placebo	67	4.9	62	3.9	33	3.9	25	3.1

No significant differences were observed.

Table 5
Analysis of Healing Rates by the Time of Endoscopy

(Domestic Placebo-Controlled Study)
"Per Protocol"

	week 0-4		week 4-6		week 6-8			
Treatment	Healing Rates	Mantel-Haenszel Chi-square p-value	Healing Rates	Mantel-Haenszel Chi-square p-value	Healing Rates	Mantel-Haenszel Chi-square p-value	Test for Interaction p-value	CMH p-vaule
Famotidine 40 mg h.s.	33/74 (45%)	0.464	16/41 (39%)	0.001	9/25 (36%)	0.981	0.03	0.031
Placebo	29/75 (39%)		4/46 (9%)		15/42 (36%)			

The dropouts were considered as not healed

The Cochran-Mantel-Haenszel (CMH) statistics controlling for time of endoscopy was computed

Table 6
Analysis of Healing Rates by the Time of Endoscopy for International Placebo Control Study

(International Placebo-Controlled Study)
"Per Protocol"

	week 0-4		week 4-6		week 6-8			
Treatment	Healing Rates	Mantel-Haenszel Chi-square p-value	Healing Rates	Mantel-Haenszel Chi-square p-value	Healing Rates	Mantel-Haenszel Chi-square p-value	Test for Interaction p-value	CMH p-vaule
Famotidine 40 mg h.s.	70/138 (51%)	0.009	27/66 (41%)	0.168	23/39 (59%)	0.000	0.11	0.000
Placebo	45/129 (35%)		22/74 (30%)		11/51 (22%)			

The dropouts were excluded in the analysis

The Cochran-Mantel-Haenszel (CMH) statistics controlling for time of endoscopy was computed

Table 7
"Equal Probability Imputation" Analysis of Healing Rates by the Time of Endoscopy

(Domestic Placebo-Controlled Study)
"Per Protocol"

	week 0-4		week 4-6		week 6-8			
Treatment	Healing Rates	Mantel-Haenszel Chi-square p-value	Healing Rates	Mantel-Haenszel Chi-square p-value	Healing Rates	Mantel-Haenszel Chi-square p-value	Test for Interaction p-value	CMH p-vaule
Famotidine 40 mg h.s.	36/74 (49%)	0.686	16/38 (42%)	0.003	9/22 (41%)	0.794	0.04	0.103
Placebo	34/75 (45%)		5/41 (12%)		16/20 (44%)			

The M-H chi-square p-value shown is p-value for comparison to placebo
The Cochran-Mantel-Haenszel (CMH) statistics controlling for time of endoscopy was computed

Table 8
"Evaluable Patients" Analysis of Healing Rates by the Time of Endoscopy

(Domestic Placebo-Controlled Study)
"Per Protocol"

	week 0-4		week 4-6		week 6-8			
Treatment	Healing Rates	Mantel-Haenszel Chi-square p-value	Healing Rates	Mantel-Haenszel Chi-square p-value	Healing Rates	Mantel-Haenszel Chi-square p-value	Test for Interaction p-value	CMH p-vaule
Famotidine 40 mg h.s.	33/68 (49%)	0.652	16/35 (46%)	0.002	9/19 (47%)	0.859	0.03	0.070
Placebo	29/65 (45%)		4/35 (11%)		15/30 (50%)			

The M-H chi-square p-value shown is p-value for comparison to placebo
The Cochran-Mantel-Haenszel (CMH) statistics controlling for time of endoscopy was computed
The dropouts are excluded in the "evaluable patients" analysis

Table 9
Cumulative Healing Rates by Average Daily Antacid Consumption

(Domestic Placebo-Controlled Study)
"Per Protocol"

4 week

Average Daily Antacid Consumption	Famotidine 40 mg H.S.	Placebo	Mantel-Haenszel Chi-square p-value	Test for interaction p-value	CMH Chi-square p-value
None	3/6 (50%)	2/9 (22%)	0.280	0.41	0.725
<1 tab	12/25 (48%)	10/16 (63%)	0.370		
1-2 tabs	5/16 (31%)	9/27 (33%)	0.889		
3 or more tabs	13/27 (48%)	8/23 (35%)	0.345		

6 week

Average Daily Antacid Consumption	Famotidine 40 mg H.S.	Placebo	Mantel-Haenszel Chi-square p-value	Test for interaction p-value	CMH Chi-square p-value
None	4/6 (67%)	3/9 (33%)	0.221	0.23	0.014
<1 tab	15/25 (60%)	10/16 (63%)	0.874		
1-2 tabs	9/16 (56%)	11/27 (41%)	0.330		
3 or more tabs	21/27 (78%)	9/23 (39%)	0.006		

8 week

Average Daily Antacid Consumption	Famotidine 40 mg H.S.	Placebo	Mantel-Haenszel Chi-square p-value	Test for interaction p-value	CMH Chi-square p-value
None	4/6 (67%)	4/9 (44%)	0.414	0.86	0.085
<1 tab	20/25 (80%)	12/16 (75%)	0.709		
1-2 tabs	12/16 (75%)	18/27 (67%)	0.570		
3 or more tabs	22/27 (81%)	14/23 (61%)	0.109		

The Mantel-Haenszel chi-square statistics and Cochran-Mantel-Haenszel statistics controlling for average daily antacid consumption were obtained by the reviewer

Table 9 (continued)
Cumulative Healing Rates by Average Daily Antacid Consumption

(Domestic Placebo-Controlled Study)
"Per Protocol"

after 8 week

Average Daily Antacid Consumption	Famotidine 40 mg H.S.	Placebo	Mantel-Haenszel Chi-square p-value	Test for interaction p-value	CMH Chi-square p-value
None	4/6 (67%)	4/9 (44%)	0.414	0.50	0.122
<1 tab	20/25 (80%)	14/16 (87%)	0.539		
1-2 tabs	13/16 (81%)	18/27 (67%)	0.308		
3 or more tabs	22/27 (81%)	14/23 (61%)	0.109		

The mantel-Haenszel chi-square statistics and Cochran-Mantel-Haenszel statistics controlling for average daily antacid consumption were obtained by the reviewer

Table 10
Selected Characteristics Of Treatment Groups at Baseline

(Domestic Ranitidine- Controlled Study)

Characteristic		Famotidine 40 mg H.S.	Ranitidine 150 mg B.I.D.
Age (Years)			
	Mean	56.8	57.1
	Median	57.5	59.0
Sex	Male	37 (39%)	35 (35%)
	Female	59 (61%)	64 (65%)
Smoking	Yes	35 (36%)	38 (38%)
	No	61 (64%)	61 (62%)
Drinking	Yes	6 (6%)	4 (4%)
	No	90 (94%)	95 (96%)
Caffeine	Yes	69 (72%)	69 (70%)
	No	27 (28%)	30 (30%)
Initial Ulcer Size (cm)			
	mean	1.29	1.25
	median	1.20	1.20
Number of Ulcers			
	1	76 (79%)	71 (72%)
	1+	20 (21%)	28 (28%)
Location*			
	Unknown	1 (1%)	1 (1%)
	Fundus	7 (7%)	2 (2%)
	Body	28 (29%)	20 (20%)
	Antrum	60 (63%)	76 (77%)
Duration of Ulcer (Years)	Mean	4.1	4.0
Other Conditions in the Esophagus*			
	Yes	24 (25%)	12 (12%)
	No	72 (75%)	87 (88%)
Gastritis			
	Yes	33 (34%)	34 (34%)
	No	63 (66%)	65 (66%)

* significant difference between treatments, p=0.05

Table 11
Crude and Kaplan-Meir Estimated Cumulative Healing Rates

(Domestic Ranitidine-Controlled Study)

"Per Protocol"

Time of Endoscopy

Treatment	Type of Estimate	N	Week 4	Week 6	Week 8	After week 8
Famotidine 40 mg H.S.	Crude	82	43 (52%)	61 (74%)	72 (88%)	74 (90%)
	Kaplan-Meier		52%	78%	93%	96%
	dropouts		5	0	0	3
Ranitidine 150 mg B.I.D.	Crude	87	46 (53%)	64 (74%)	74 (85%)	74 (85%)
	Kaplan-Meier		53%	77%	91%	91%
	dropouts		6	0	0	7

No statistically significant difference was observed between treatments at any time period with respect to either the crude or life-table estimates of the ulcer healing rates.

Table 12

Frequency and Percent of Patients with Ulcer Healed After Week 8 Stratified by Selected Factors

(Domestic Ranitidine-Controlled Study)

"Per Protocol"

Factor	Level	Famotidine 40 mg H.S.	Ranitidine 150 mg B.I.D.
Ulcer size (cm)	0.5-0.95	23/26 (89%)	31/33 (94%)
	1.00-1.45	18/20 (90%)	15/20 (75%)
	1.50-	33/36 (92%)	28/34 (82%)
Smoking	No	47/53 (89%)	45/55 (82%)
	Yes	27/29 (93%)	29/32 (91%)
Drinking	No	71/78 (91%)	70/83 (84%)
	Yes	3/4 (75%)	4/4 (100%)
Antacid use	No	12/14 (86%)	12/17 (71%)
	Yes	62/68 (91%)	62/70 (89%)
Esophagus conditions	No	56/61 (92%)	63/75 (84%)
	Yes	17/20 (85%)	11/12 (92%)
Duodenal conditions	No	59/65 (91%)	59/69 (86%)
	Yes	14/16 (88%)	15/18 (83%)
Age group	under 40	10/12 (83%)	11/13 (85%)
	40-59	28/33 (85%)	31/33 (94%)
	60 or over	36/37 (97%)	32/41 (78%)
Pre-day pain	None	9/11 (82%)	16/19 (84%)
	Mild	18/21 (86%)	14/19 (74%)
	Moderate	29/30 (97%)	24/25 (96%)
	Severe	18/20 (90%)	20/24 (83%)
Pre-night pain	None	19/22 (86%)	28/31 (90%)
	Mild	18/21 (86%)	16/21 (76%)
	Moderate	20/20 (100%)	19/21 (91%)
	Severe	17/19 (90%)	11/14 (79%)
Caffeine	No	18/22 (82%)	21/28 (75%)
	Yes	56/60 (93%)	53/59 (90%)
No. of ulcers	single	57/65 (88%)	53/63 (84%)
	multiple	17/17 (100%)	21/24 (88%)
Gastritis	No	49/55 (89%)	49/58 (85%)
	Yes	24/26 (92%)	25/29 (86%)

Table 13
Factors Related to Ulcer Healing

(Domestic Ranitidine-Controlled Study)

"Per Protocol"

Factor	Comparison	Percent Healed	Time to Healing
Initial Ulcer Size	0.50-0.95 vs 1.00-1.45	NS	p=0.003
	0.50-0.95 vs 1.50-2.50	NS	P<0.001
Pre-Day Pain	Moderate vs None	p=0.042	NS
	Moderate vs Mild	p=0.011	NS
Pre-Night Pain	Moderate vs Mild	p=0.046	NS
Caffeine	Yes vs No	p=0.018	NS
Gastritis	Yes vs No	NS	

First of each pair of comparison had higher percent healed.

Table 14
Daytime and Nighttime Pain Relief for the Treatment Groups at the End of Study

(Domestic Ranitidine-Controlled Study)

"Per Protocol"

	Famotidine 40 mg H.S.	Ranitidine 150 mg B.I.D.
Daytime pain		
No. of patients without pain	57/74 (77%)	60/76 (79%)
Median time (days) to pain relief	19	20
Nighttime pain		
No. of patients without pain	58/71 (82%)	58/74 (78%)
Median time (days) to pain relief	20	21

No significant between group difference was observed with respect to time to pain relief.

Table 15
Antacid Consumption by Treatment Groups

(Domestic Ranitidine-Controlled Study)

"All Patients Treated"

Statistics	Treatment	(N)	Week 1	(N)	Week 4	(N)	Week 6	(N)	Week 8
Mean No. of Antacid Tablets	Famotidine 40 mg H.S.	77	2.41	73	1.36	30	1.33	13	0.56
	Ranitidine 150 mg B.I.D.	79	2.35	75	1.54	31	1.22	16	1.37
Mean Days of Antacid Therapy	Famotidine 40 mg H.S.	77	4.7	73	2.6	30	2.5	13	1.4
	Ranitidine 150 mg B.I.D.	79	4.0	75	2.6	31	2.7	16	2.1

No significant differences were observed.

Table 16
Crude and Kaplan-Meier Estimated Cumulative Healing Rates

(International Placebo-Controlled Study)

"Per Protocol"

Time of Endoscopy

Treatment	Type of Estimate	N	Week 4 Healing Rates	p-value	Week 6 Healing Rates	p-value	Week 8 Healing Rates	p-value	After week 8 Healing Rates	p-value
Famotidine 40 mg H.S.	Crude	149	70 (47%)	0.006	97 (65%)	0.001	120 (80%)	0.000	120 (80%)	0.000
	Kaplan-Meier		47%		68%		87%		87%	
	dropouts		11		2				0	
Placebo	Crude	145	45 (31%)		67 (46%)		78 (54%)		80 (55%)	
	Kaplan-Meier		31%		49%		60%		62%	
	dropouts		16		10		1		0	

2-tail Fisher's exact test p-values were obtained by reviewer for comparisons to placebo for crude healing rates

Table 17
"Equal Probability Imputation" Analysis of Cumulative Healing Rates

(International Placebo-Controlled Study)

"Per Protocol"

Treatment	cum week 4 Healing Rates	Mantel-Haenszel Chi-square p-value	cum week 6 Healing Rates	Mantel-Haenszel Chi-square p-value	cum week 8 Healing Rates	Mantel-Haenszel Chi-square p-value
Famotidine 40 mg h.s.	75/149 (50%)	0.017	103/149 (69%)	0.014	126/149 (85%)	0.000
Placebo	53/145 (37%)		80/145 (55%)		91/145 (63%)	

The p-value shown is p-value for comparison to placebo

Table 18
"Evaluable Patients" Analysis of Cumulative Healing Rates

Controlled St

(International Placebo-Controlled Study)

"Per Protocol"

Treatment	cum week 4 Healing Rates	Mantel-Haenszel Chi-square p-value	cum week 6 Healing Rates	Mantel-Haenszel Chi-square p-value	cum week 8 Healing Rates	Mantel-Haenszel Chi-square p-value
Famotidine 40 mg h.s.	70/138 (51%)	0.009	97/136 (71%)	0.013	120/136 (88%)	0.000
Placebo	45/129 (35%)		67/119 (56%)		78/118 (66%)	

The p-value shown is p-value for comparison to placebo

The dropouts are excluded in the "evaluable patients" analysis

Statistical Rev.

N19462

STATISTICAL REVIEW AND EVALUATION

Date: OCT - 3 1991

NDA #: NDA 19-462/S-010

Applicant: Merck Sharp and Dohme Research Laboratories

Name of Drug: Pepcid (Famotidine) Tablet

Indications: Acute Symptomatic Relief in Patients with GERD

Documents Reviewed: NDA Vol. 1, 14-29, Dated May 24, 1990
NDA Supp. Amendment Dated June 8, 1990
NDA Supp. Amendment Vol. 29a Dated June 12, 1990
NDA Supp. Amendment Dated August 30, 1990
NDA Supp. Amendment Dated September 19. 1990
NDA Supp. Amendment Dated June 17, 1991
NDA Supp. Amendment Dated July 25, 1991

Medical Reviewer: Andre Dubois, M.D.

This review is for symptomatic relief trials (protocols #009 and #010). A separate review is attached for esophageal healing trials (protocols #013 and #588).

A. Background

Famotidine was approved and used in the United States for the treatment of active duodenal ulcer and acute benign gastric ulcer. In this NDA supplement, the sponsor seeks approval for the efficacy of famotidine for the treatment of acute symptomatic and erosive gastroesophageal reflux disease (GERD).

The sponsor proposed two famotidine dosing regimens: a dosing regiment of 20 mg b.i.d. is proposed for the symptomatic treatment of patients with GERD, and a dosing regiment of 40 mg b.i.d. is proposed for the treatment of GERD when accompanied by endoscopically verified erosion or ulceration of the esophageal mucosa.

The sponsor has submitted four multicenter efficacy trials (protocols #009, #010, #013, and #588) in support of these proposed claims. Two trials (protocols #009 and #010) were conducted to demonstrate symptom relief in patients with GERD, and two trials (protocols #013 and #588) were conducted to establish efficacy in healing of endoscopically verified esophageal erosion or ulceration in patients with GERD.

This review is for symptomatic relief trials (protocols #009 and #010). A separate review is attached for the esophageal healing trials (protocols #013 and #588).

Symptomatic Relief Trials

Two trials (protocols #009 and #010) were designed to demonstrate that famotidine treatment relieves symptoms in GERD patients. Symptoms were measured similarly in both studies. Patients assessed symptom relief by

assigning a global symptomatic improvement score at scheduled visits. They also recorded daytime and nighttime heartburn relief in a daily diary.

Patients with a history of GERD symptoms entered both studies. Patients were to undergo endoscopy at baseline. In protocol #009, patients who had erosive or ulcerative lesions of the esophagus were excluded. In protocol #010, patients who had erosive or ulcerative lesions of the esophagus were permitted to enter; however, the randomization in this study was stratified to balance the treatment groups for this factor.

B. Protocol No. 009

1. Description of Study

The study was a double-blind, randomized, parallel, placebo-controlled, multi-center (21 investigators),dose ranging study. The objective of this study was to evaluate the effects of famotidine 40 mg h.s. and 20 mg b.i.d as compared to the placebo in the symptomatic relief of patients with symptoms of gastroesophageal reflux with a normal esophagus or mild endoscopic esophagitis over a period of six weeks.

The study had a one-week placebo baseline period followed by a six-week treatment phase. Patients admitted to the study were to have a history of heartburn for approximately 15 out 30 days prior to the placebo baseline period, had a positive Bernstein test, and had endoscopically proven normal esophageal mucosa (grade 0) or evidence of mild esophagitis (grade 1) defined as erythema or hyperemia but without erosions. Patients who had heartburn for 5 to 7 days of the placebo baseline period were randomized to the three treatment groups (placebo, famotidine 20 mg b.i.d., and famotidine 40 mg h.s.).

Patients were advised to avoid foods which could exacerbate the symptoms of their disease. Patient were encouraged to limit their consumption of caffeine, alcohol, and tobacco.

Patients were asked to record daytime heartburn, nighttime heartburn, and global assessment daily in the diary. Patients rated their severity of daytime heartburn, nighttime heartburn, acid regurgitation, and dysphagia symptoms daily for one-week placebo baseline period, and throughout the six-week post-randomized study period. All symptoms were rated on a 0-4 scale (0=no, 1=mild, 2=moderate, 3=severe, 4=disabling).

Patient's global response and time-to-relief of heartburn were primary efficacy parameters. Patient's global response was assessed at weeks 2 and 6. Each patient rated improvement on a 0-3 scale (0=no improvement, 1=slight improvement, 2=moderate improvement, and 3=excellent improvement). Time-to-relief of heartburn was defined as the day of the study on which the patient has a severity scores of 0 (none) with no recurrence of heartburn later on.

A patient was considered a therapeutic success if the patient was heartburn-free for at least 5 of the last 7 days immediately prior to the

scheduled visit. Additionally, if the patient had heartburn for less than or equal to 2 days during this visit, the heartburn must be mild (severity score 1).

For sample size calculations, the expected percentages of patients becoming heartburn-free after six weeks of therapy with placebo, famotidine 40 mg h.s. and famotidine 20 mg b.i.d. were taken as 40%, 70%, and 85%, respectively. The sample sizes of 120 patients for each active treatment group and 60 patients for the placebo were determined to detect at least a 30% difference in the proportion of heartburn-free patients between the famotidine groups and placebo with 95% power, and a 15% difference in the proportion of heartburn-free patients between the two famotidine groups with 80% power, testing at 5% level of significance with a two-tailed test.

2. Sponsor's Analysis

A total of 389 patients were randomized according to an allocation 2:2:1 by design into the famotidine 40 mg h.s., the famotidine 20 mg b.i.d., the placebo treatment groups. One hundred fifty-five patients were allocated to famotidine 40 mg h.s., 158 patients to famotidine 20 mg b.i.d., and 76 patients to placebo.

The treatment groups were generally comparable at baseline with respect to various pertinent patient characteristics such as age, sex, race, smoking, drinking, caffeine, history of dysphagia, history of acid regurgitation, esophagitis grade, daytime severity of heartburn, nighttime severity of heartburn and etc. (see Table 1). Pairwise comparisons indicated that at baseline, the famotidine 40 mg h.s. group experienced significantly greater daytime heartburn than did the placebo group. Also, marginally significant differences ($0.05 < p < 0.01$) at baseline were found as follows:

(1) between the famotidine 20 mg b.i.d. group and the placebo group for sex, alcohol, and abnormalities in the esophagus,

(2) between the famotidine 40 mg h.s. group and the famotidine 20 mg b.i.d. group for alcohol and abnormalities in the duodenum.

Efficacy analyses were done on two data sets: the "per protocol" and the "all patients treated" data sets. The former excluded all patients who were protocol violators and the latter included all randomized patients who had baseline and post-randomization treatment period data. In both analyses, if a patient dropped out of the study early, or did not record data for a particular time period, the last valid measurement was carried forward to the missing timepoint(s).

Patients excluded from the "per protocol" analyses were:

1) Patients who took greater than 30 Gelusil tablets during the baseline week, or weeks 1 through 6.

2) Patients who had taken a therapeutic dose of H_2-receptor antagonists (cimetidine >=800 mg daily, ranitidine >=300 mg daily, famotidine >=40 mg daily) for more than five consecutive days during the two weeks prior to the placebo baseline period.

3) Patients who took nonsteroidal anti-inflammatory drugs or other H_2-blockers.

The number of patients included in analyses of the primary efficacy variables according to the intent-to-treat and the "per protocol" analyses were tabulated below:

	Fam 40 mg h.s.	Fam 20 mg b.i.d.	Placebo
Total Randomized	155	158	76
Global Evaluation			
Week 2 ITT	147	153	72
Week 6 ITT	149	154	73
Week 2 Per Protocol	102	103	47
Week 6 Per Protocol	101	105	46
Relief of Daytime/ Nighttime Heartburn			
ITT	148	154	74
Per Protocol	106	106	50

2.1 Results for the Primary Efficacy Variables

Primary efficacy variables were patient's global response and complete reliefs of daytime heartburn and nighttime heartburn.

2.1.1 Results for Patient's Global Evaluation

Global evaluations were compared among treatments over the distribution of the four global assessment categories (no improvement, slight, moderate or excellent improvement) at weeks 2 and 6 in the "all patients treated" and the "per-protocol" analyses. The detailed results are given in Table 2. The main results are summarized in the following table:

Results for Patient's Global Evaluation
Famotidine 40 mg HS and 20 mg BID vs Placebo

Week 2

	All Patients Treated		Per Protocol	
Comparison	Mean Scale	2-tailed p-value	Mean Scale	2-tailed p-value
Fam 40 mg HS	1.70	0.039	1.79	0.494
vs				
Placebo	1.44		1.68	
Fam 20 mg BID	1.85	0.002	1.97	0.048
vs				
Placebo	1.44		1.68	

Week 6

	All Patients Treated		Per Protocol	
Comparison	Mean Scale	2-tailed p-value	Mean Scale	2-tailed p-value
Fam 40 mg HS	1.83	0.009	1.97	0.973
vs				
Placebo	1.60		2.02	
Fam 20 mg BID	2.18	0.000	2.30	0.210
vs				
Placebo	1.60		2.02	

Note: the above pairwise 2-sided p-values are not adjusted for multiple comparisons. Mean scale was computed by this reviewer using scale: 0=no improvement; 1=slight improvement; 2=moderate improvement; 3=excellent improvement.

Thus, the results for the patients' global evaluations were as follows:

1) The famotidine 20 mg b.i.d. group was significantly better than the placebo in term of the distribution of the four assessment categories at weeks 2 and 6 from the "all patients treated" analysis and at only week 2 from the "per protocol" analysis.

2) The famotidine 40 mg h.s. group was significantly better than the placebo in term of the distribution of the four assessment categories at weeks 2 and 6 from the "all patients treated" analysis but not from "per protocol" analysis.

3) The famotidine 20 mg b.i.d. group was not significantly different from the famotidine 40 mg h.s. group in term of the distribution of the four assessment categories at weeks 2 and 6 from both "all patients treated" "per protocol" analyses (see Table 2). [The result may be due to lack of statistical power.]

The sponsor also analyzed global evaluations by collapsing the four assessment categories into two: successful evaluation (moderate or excellent improvement) or unsuccessful evaluation (no or slight improvement). The results are given in Table 3. The main results are summarized in the following table.

Results for Successful/Unsuccessful Evaluation
(Famotidine 40 mg HS and 20 mg BID vs Placebo)

Week 2

	All Patients Treated			Per Protocol		
Comparison	Succ. Rate		2-tailed p-value	Succ. Rate		2-tailed p-value
Fam 40 mg HS vs Placebo	83/147	(56%)	0.389	62/102	(61%)	1.000
	36/72	(50%)		28/47	(60%)	
Fam 20 mg BID vs Placebo	107/153	(70%)	0.005	79/103	(77%)	0.051
	36/72	(50%)		28/47	(60%)	

Week 6

	All Patients Treated			Per Protocol		
Comparison	Succ. Rate		2-tailed p-value	Succ. Rate		2-tailed p-value
Fam 40 mg HS vs Placebo	102/149	(68%)	0.365	73/101	(72%)	0.544
	45/73	(62%)		36/46	(78%)	
Fam 20 mg BID vs Placebo	126/154	(82%)	0.002	90/105	(86%)	0.341
	45/73	(62%)		36/46	(78%)	

Note: the above pairwise 2-sided p-values are not adjusted for multiple comparisons.

The results for successful/unsuccessful evaluations were as follows:

1) The famotidine 20 mg b.i.d. group was significantly better than the placebo in term of the proportion of successful evaluation at weeks 2 and 6 from the "all patients treated" analysis but at only week 2

from the "per protocol" analysis.

2) The famotidine 20 mg b.i.d. group was significantly better than the famotidine 40 mg h.s. group at weeks 2 and 6 from both "all patient treated" and "per protocol" analyses (see Table 3).

3) The famotidine 40 mg h.s. group was not significantly different from placebo at weeks 2 and 6 from both "all patient treated" and "per protocol" analyses. The famotidine 40 mg h.s. group was numerically worse than the placebo at week 6 in "per protocol" analysis.

Overall, the proportion of patients with successful global evaluations combined over the three treatment groups was greater in the "per protocol" analysis than in the "all patients treated" analysis for all three treatment groups.

2.1.2 Results for Complete Relief of Daytime Heartburn and Nighttime Heartburn

Relief/no relief at the end of study was analyzed for daytime heartburn and nighttime heartburn using Fisher's exact test. Patients with a baseline severity of none were included in the analyses. Because a patient may have a baseline score of "none", and then that patient may have had experienced symptoms during the treatment period of the study. Eliminating such patients from the analyses would eliminate a significant number of symptomatic patients. Dropouts were considered to be relieved if they were relieved at the time of withdrawal. Patients with no treatment period data were considered to be "not relieved" at the end of the study for the relief/no relief analysis.

The results of complete relief of daytime heartburn and nighttime heartburn symptoms by the end of study are given in Table 4. The main results are summarized in the following table.

Results for Complete Relief of Daytime Heartburn and Nighttime Heartburn
(Famotidine 40 HS and 20 BID vs Placebo)

Complete Relief of Daytime Heartburn

	All Patients Treated		Per Protocol	
Comparison	Relief Rate	2-tailed p-value	Relief Rate	2-tailed p-value
Fam 40 mg HS	71/155 (46%)	0.323	54/110 (49%)	0.502
vs				
Placebo	29/76 (38%)		22/51 (43%)	
Fam 20 mg BID	94/158 (60%)	0.003	74/108 (69%)	0.003
vs				
Placebo	29/76 (38%)		22/51 (43%)	

Complete Relief of Nighttime Heartburn

Comparison	All Patients Treated Relief Rate	2-tailed p-value	Per Protocol Relief Rate	2-tailed p-value
Fam 40 mg HS vs Placebo	86/155 (56%) 40/76 (53%)	0.779	65/110 (59%) 32/51 (63%)	0.730
Fam 20 mg BID vs Placebo	107/158 (68%) 40/76 (53%)	0.030	79/108 (73%) 32/51 (63%)	0.199

The results for complete relief of daytime heartburn and nighttime heartburn at the end of study were as follows:

For daytime heartburn:

1) The famotidine 20 mg b.i.d. group was significantly better than both the famotidine 40 mg h.s. and the placebo with respect to the proportion of patients completely relieved of daytime heartburn symptoms by the end of study from both "all patients treated" and "per protocol" analyses (see Table 4).

2) The famotidine 40 mg h.s. group was not significantly different from the placebo for complete relief of daytime heartburn from both "all patients treated" and "per protocol" analyses.

For nighttime heartburn:

1) The famotidine 20 mg b.i.d. group was significantly better than both the famotidine 40 mg h.s. group and the placebo for complete relief of nighttime heartburn from the "all patients treated" analysis. But, the famotidine 20 mg b.i.d. group could not be shown to be significantly different from the placebo, but was significantly better than the famotidine 40 mg h.s. group from the "per protocol" analysis (see Table 4).

2) The famotidine 40 mg h.s. group was not significantly different from placebo for complete relief of nighttime heartburn from both "all patients treated" and "per protocol" analyses. As a matter of fact, numerically the famotidine 40 mg h.s. group was noted to be worse than the placebo for complete relief of nighttime heartburn from the "per protocol" analysis.

The time-to-complete symptom relief and no recurrence (score of 0) was assessed using the Mantel-Haenszel life-table methods, stratifying on average baseline score. Patients with no treatment period data or no baseline values were not included in the time-to-complete relief analysis. The results are given in Table 5, The results are as follows:

For daytime heartburn:

1) The famotidine 20 mg b.i.d. group was significantly better than both the famotidine 40 h.s. group and the placebo in term of time-to-relief of daytime heartburn from both "all patients treated" and "per protocol" analyses (see Table 5).

2) The famotidine 40 mg h.s. group was not significantly different from the placebo in term of time-to-relief of daytime heartburn from both "all patients treated" and "per protocol" analyses.

For nighttime heartburn:

1) The famotidine 20 mg b.i.d. group was could not be shown to be significantly different from the placebo in term of time-to-relief of nighttime heartburn from both "all patients treated" and "per protocol" analyses. However, the famotidine 20 mg b.i.d. group was significantly better than the famotidine 40 h.s. group in term of time-to-relief of nighttime heartburn from the "per protocol" analysis but not from the "all patient treated" analysis.

2) The famotidine 40 mg h.s. group was not significantly different from the placebo in term of time-to-relief of nighttime heartburn from both "all patients treated" and "per protocol" analyses.

Thus, for the famotidine 20 mg b.i.d. group, there were consistent results in relief of daytime heartburn but not for the nighttime heartburn.

2.2 Results for Secondary Efficacy Variables

Secondary efficacy variables were complete relief of dysphagia and acid regurgitation, and antacid consumption.

Relief/no relief at the end of study was analyzed for dysphagia and acid regurgitation using Fisher's exact test. The results are given in Table 4.

Average daily antacid consumption was calculated for each patient as the total number of antacids taken during the study divided by the total number of days the patient was in the study.

The results for secondary efficacy variables were as follows:

1) For complete relief of dysphagia and acid regurgitation, there were no treatment differences in both "all patient treated" and "per protocol" analyses.

2) The famotidine 20 mg b.i.d. group used significantly less antacids than did the placebo group in term of median average daily antacid consumption (0.73 vs 1.44, $p<0.01$).

3. Reviewer's Evaluation (Protocol #009)

3.1 Re-analysis of Patient's Global Evaluation

It was found that the sponsor used wrong scales for analyzing patient's global evaluation. The scales used by the sponsor were: 0 - no improvement, 6 - slight improvement; 7 - moderate improvement, and 8 - excellent improvement. According to the protocol, the scales should be 0 - 3 (0 - no improvement. 1 - slight, 2 - moderate, and 3 - excellent). This reviewer reanalyzed the patient's global evaluation after correcting the scales on using the same method the sponsor used, Cochran-Mantel-Haenszel (CMH) test, and the nonparametric methods (Wilcoxon rank sum test and Kruskal-Wallis test). The results are given in Table 6. As seen from Table 6, the results from the nonparametric method are generally similar to those from the CMH method in term of significance. However, contrary to the sponsor's finding, the famotidine 20 mg b.i.d. group was significantly better than the famotidine 40 mg h.s. group at week 6 from both "all patients treated" and "per protocol" analyses. The famotidine 40 mg h.s. group was not significantly different from the placebo at weeks 2 and 6 from the "all patients treated" analysis.

Hence, in this reviewer's evaluation, the famotidine 20 mg b.i.d. group was significantly better than the famotidine 40 mg h.s. group in term of global evaluation at weeks 2 and 6 in the following manner:

1) For the "all patient treated" analysis, the famotidine 20 mg b.i.d group was superior to the placebo in term of global evaluation at both weeks 2 and 6; the famotidine 40 mg h.s. group was marginally significantly better than the placebo only at week 2.

2) For the "per protocol" analysis, the famotidine 20 mg b.i.d. group was only slightly significantly better than the placebo only at week 2; the famotidine 40 mg h.s. group was not significantly different from the placebo.

A weaker result in favor of famotidine 20 mg b.i.d. for the "per protocol" analysis is due the fact that the censoring pattern for the placebo group is different from that for the famotidine 20 mg b.i.d. group. More patients with scale value of 0 and 1 (no improvement or slight improvement) in global evaluation withdraw in the placebo group in comparison to the famotidine 20 mg b.i.d. group; The table in the next section (Section 3.2) summaries the frequency of patients carried forward from week 2 for the "all patient treated" and the "per protocol" analyses. Thus dropouts were handled differently for the two type of analyses. That would also contribute a weaker result for the famotidine 20 mg group in the "per protocol" analysis. The fact that there was more censoring in the placebo group in patients who showed "no" or "slight" improvement in global evaluation indicates lack of efficacy for this treatment group in comparison to the famotidine 20 mg b.i.d. group.

3.2 Comments for Patient's Global Evaluation

In the sponsor's analyses of patient's global evaluation, if a patient

dropped out of the study early or did not record data for week 6, the measurement for the week 2 was carried forward to that for the week 6. There were disproportionate number of patients having data carried forward from week 2 among the treatment groups: 15/149 for famotidine 40 mg h.s., 4/154 for famotidine 20 mg b.i.d., and 9/73 for placebo. Among patients having data carried forward from week 2, famotidine 20 mg b.i.d. group had more patients with scales 2 or 3 at week 2 in comparison to the other two treatment groups as seen in the table below.

Patients with Data Carried forward from Week 2

(All Patients Treated Analysis)

	Moderate or Excellent Improvement	No or Slight Improvement	Total
Famotidine 40 mg h.s.	4	11	15
Famotidine 20 mg b.i.d.	2	2	4
Placebo	1	8	9

(Per Protocol Analysis)

	Moderate or Excellent Improvement	No or Slight Improvement	Total
Famotidine 40 mg h.s.	4	2	6
Famotidine 20 mg b.i.d.	2	0	0
Placebo	1	0	0

This reviewer reanalyzed patient's global evaluation week 6 data excluding patients which had measurement carried forward from the week 2. The results are given in Table 7 for patient's global evaluation. The main results are summarized in the following table.

P-values for Analysis of Patient's Global Evaluation at Week 6

(ALL Patients Treated)

	Carried Forward from Week 2		No Carried Forward from Week 2	
	vs FAM 20 b.i.d.	vs Placebo	vs FAM 20 b.i.d.	vs Placebo
FAM 40 mg h.s.	0.020	0.110	0.015	0.312
FAM 20 mg b.i.d.		0.000		0.006

(Per Protocol)

	Carried Forward from Week 2 vs FAM 20 b.i.d.	Carried Forward from Week 2 vs Placebo	No Carried Forward from Week 2 vs FAM 20 b.i.d.	No Carried Forward from Week 2 vs Placebo
FAM 40 mg h.s.	0.008	0.752	0.017	0.628
FAM 20 mg b.i.d.		0.068		0.146

As seen from the table above, the week 6 global evaluation results using "no carried forward from week 2" were similar to those from the sponsor's analysis using "carried forward from week 2" in terms of significance from both "all patients treated" and "per protocol" analyses. However, some difference was noted by "per protocol" analysis for the famotidine 20 mg b.i.d. vs. placebo comparison, p=0.068 with carried forward analysis as compared to p=0.146 with no carried forward analysis.

3.3 Comments for Complete Relief of Daytime Heartburn and Nighttime Heartburn

In the sponsor's analyses of complete relief of daytime heartburn and nighttime heartburn at the end of study, patients with a baseline severity of none were included in the analyses. This reviewer performed alternative analyses of relief/no relief daytime heartburn and nighttime heartburn for those patients had baseline score other than "none". This analysis also excluded patients with no treatment score data or missing observation. The results are given in Table 8. The main results are summarized in the following table.

P-values for Analyses of Complete Relief of Heartburn at the End of Study

(All Patients Treated)

	Sponsor's Analysis						Reviewer's Analysis		
	Complete Relief			Time-to-Relief			Complete Relief		
	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC
Daytime Heartburn	0.018	0.323	0.003	0.01	0.66	0.02	0.027	0.315	0.004
Nighttime Heartburn	0.028	0.779	0.030	0.12	0.63	0.16	0.186	0.156	0.011

(Per Protocol)

	Sponsor's Analysis						Reviewer's Analysis		
	Complete Relief			Time-to-Relief			Complete Relief		
	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC
Daytime Heartburn	0.004	0.502	0.003	0.00	0.14	0.00	0.078	0.168	0.004
Nighttime Heartburn	0.032	0.730	0.199	0.03	0.57	0.07	0.104	0.705	0.106

As seen from the table above, there were consistent results favoring famotidine 20 mg b.i.d to placebo for relieving daytime heartburn.

3.4 Comments for Antacid Consumption

There was a problem of antacid consumption. Nearly 1/2 of the patients excluded from the "per protocol" analysis were patients who exceeded the Gelusil limit of 30 tablets per week during at least 1 week of the study.

As requested by this reviewer, the sponsor assessed the effect of antacid consumption on global assessment and heartburn relief. The average daily number of antacid tablets taken was calculated for each patient by dividing the total number of antacids taken during the study by the total number of days the patient was in the study. Each patient was then further classified into one of the following three categories:

Daily Number of Antacid Tablets taken = 0
Daily Number of Antacid Tablets greater than 0 and less than or equal to 2.
Daily Number of Antacid Tablets greater than 2

The analysis of global assessment and relief, no relief heartburn were then adjusted for these three levels of antacid consumption. When adjusting for average daily antacid consumption, the overall significance were maintained and the results did not change.

This reviewer used Kruskal-Wallis test to compare the antacid consumption among treatment groups by week. The results revealed that significant difference for antacid usage was observed only at week 1 and there was no significant difference of antacid consumption among treatments beyond week 1.

Also, the data indicate that for this study average daily antacid consumption has statistically significant ($P<0.05$) relationship to the proportion of patients with global evaluation rating of moderate or excellent improvement and patients completely relieved of daytime heartburn and nighttime heartburn. That is, patients with moderate to excellent improvement in the global evaluation tend to use less antacid consumption than patients with "no" or "slight" improvement. Patients with completely relieved of daytime heartburn and nighttime heartburn tend to use less antacid than patients with no completely relieved of daytime heartburn and nighttime heartburn.

C. Protocol No. 010

1. Description of Study

The study was double-blind, randomized, parallel, placebo-controlled, multi-center (20 investigators) dose ranging study. The objective of this study was to evaluate the effects of famotidine 40 mg h.s. and 20 mg b.i.d. as compared to the placebo in the symptomatic relief and healing of patients with GERD over a period of six to twelve weeks.

Patients with a diagnosis of gastroesophageal disease who had heartburn characterized by retrosternal burning pain were selected for this study. Heartburn had to have been present for approximately 15 out of 30 days prior to entering the study.

Both erosive esophagitis (Endoscopic Grade 2-4) and non-erosive esophagitis (Endoscopic Grade 0 or 1) patients were eligible to enter the trial. However, patients without erosive esophagitis had to have a positive Bernstein test.

Patients who satisfied the entrance criteria and who had none of exclusion criteria were stratified for the presence or absence of erosive esophagitis as demonstrated endoscopically and were randomized into the study. Patients with erosive esophagitis were randomized immediately following an endoscopic evaluation, whereas patients without erosive esophagitis were randomized following the completion of the 1-week placebo baseline period, and then only if the patients had 5 symptomatic heartburn days during the 1-week placebo baseline period.

The treatment period was 6 to 12 weeks for erosive esophagitis patients and only 6 weeks for non-erosive esophagitis patients. Patients were seen in the clinic at weeks 2 and 6. An erosive esophagitis patient was also seen in the clinic at week 12 unless the patient's erosive esophagitis was healed at week 6.

Endoscopy was performed at baseline for non-erosive esophagitis patients. Endoscopies for erosive esophagitis patients were done at baseline and at the end of treatment weeks 6 and 12, if the erosive esophagitis was not healed at a prior endoscopy.

Healing was defined as Grade 0 or 1. Ulcer and erosions had to be healed, if both were present. However, regression of Barrett's epithelium was not required for healing.

The patients were asked to record daily in the diary on a scale of 0 to 4, daytime heartburn and nighttime heartburn, intensity of associated GI symptoms, and global assessment. Gelusil tablets were dispensed at each visit to be taken for heartburn as needed, but were not to exceed 30 tablets/week including the 1-week baseline placebo period.

A patient was considered a therapeutic success if the patient was heartburn-free for at least 5 of the last 7 days immediately prior to the scheduled visit and only if any existing heartburn was mild in nature (severity scale 1).

Patient's global assessment and time-to-relief of heartburn were the two most important primary efficacy parameters. Secondary efficacy parameters were number of heartburn episodes and number of healed erosive esophagitis patients. Patient's global assessment was evaluated at weeks 2 and 6. In addition, patient's global assessment was evaluated at week 12 for erosive esophagitis patients who were not healed at week 6. Time-to-relief of heartburn was defined as the day of the study on which the patient had a severity score of 0 (none) with no reoccurrence of heartburn later on.

The proportion of patients whose erosive esophagitis had healed (cumulatively) at each timepoint was compared between treatment groups. The cumulative crude healing rates were assessed pairwisely among treatments using Fisher's Exact test at weeks 6, 12, and after week 12. Dropouts were considered to be not healed. A life-table analysis was done to assess time-to-healing. The Mantel-Haenszel method was used to test between-group differences.

The study was designed to detect at least a 30% difference in the proportion of heartburn-free patients (40% vs 70%) between the famotidine groups and the placebo group with 95% power, and to detect a 15% difference in the proportion of heartburn-free patients (70% vs 85%) between the two famotidine treatment groups with 80% power.

2. Sponsor's Study Results

A total of 338 patients were randomized according to an allocation 2:2:1 by design into the famotidine 40 mg h.s., the famotidine 20 mg b.i.d., and the placebo; one hundred thirty-five patients were allocated to famotidine 40 mg h.s., 137 patients to famotidine 20 mg b.i.d., and 66 patients to placebo.

The treatment groups were generally comparable at baseline with respect to various pertinent patient characteristics such as age, sex, race, smoking, drinking, caffeine, history of dysphagia, history of acid regurgitation, esophagitis grade, daytime severity of heartburn, nighttime severity of heartburn and etc. (see Table 9).

Efficacy analysis was done on two data sets: the "per protocol" and the "all patients treated" data sets. The former excluded all patients who were protocol violators and the latter included all randomized patients who had baseline and treatment period data. In both analyses, if a patient dropped out the study early, the last valid measurement was carried forward to subsequent timepoints. However, for the "per protocol" analysis of global evaluations, acceptable day ranges were established (as below). As a result, values were not carried forward in the following cases:

1. If a global evaluation was out of range at week 2 and/or week 6, it was not carried forward for imputing a week 6 or 12 (respectively) missing value.

2. If a global evaluation was out of range at week 6, it was not replaced by the previous visit's measurement.

Acceptable day ranges for the "per protocol" analysis for global evaluation were defined as follows.

Global Evaluation Week	Day Specified in Protocol	Acceptable Day Range
Week 2	14	10-18
Week 6	42	35-49
Week 12	84	77-91

The number of patients included in analyses of the primary efficacy variables for the intent-to-treat analysis and the "per protocol" analysis are tabulated below.

	FAM 40 mg h.s.	FAM 20 mg b.i.d.	Placebo
Total Randomized	135	137	66
Global Evaluation			
Week 2 ITT	129	131	62
Week 6 ITT	129	131	62
Week 2 Per Protocol	83	87	31
Week 6 Per Protocol	83	86	31
Week 12 Per Protocol	79	84	30

Relief of Daytime/ Nighttime Heartburn			
ITT	131	133	63
Per Protocol	83	88	31

2.1 Results for the Primary Efficacy Variables

Primary efficacy variables were patient's global response and complete reliefs of daytime heartburn and nighttime heartburn.

2.1.1 Results for Patient's Global Evaluation

Global evaluations were compared among treatments over the distribution of the four global assessment categories (no improvement, slight, moderate or excellent improvement) at weeks 2, 6 and 12 in the "all patients treated" and the "per-protocol" analyses. The results are given in Table 10 . The main results are summarized in following table.

Week 2

	All Patients Treated		Per Protocol	
Comparison	Mean Scale	2-tailed p-value	Mean Scale	2-tailed p-value
Fam 40 mg HS vs Placebo	1.58 0.94	< 0.001	1.65 1.26	0.043
Fam 20 mg BID vs Placebo	1.74 0.94	< 0.001	1.80 1.26	0.002

Week 6

	All Patients Treated		Per Protocol	
Comparison	Mean Scale	2-tailed p-value	Mean Scale	2-tailed p-value
Fam 40 mg HS vs Placebo	1.74 1.18	< 0.001	1.83 1.39	0.037
Fam 20 mg BID vs Placebo	1.96 1.18	< 0.001	2.05 1.39	0.001

Week 12

Comparison	All Patients Treated Mean Scale	2-tailed p-value	Per Protocol Mean Scale	2-tailed p-value
Fam 40 mg HS	1.83	0.002	1.94	0.074
vs				
Placebo	1.32		1.53	
Fam 20 mg BID	2.02	< 0.001	2.10	0.005
vs				
Placebo	1.32		1.53	

Note: Mean scale was computed by this reviewer using scale: 0=no, 1=slight, 2=moderate, and 3=excellent.

The results for patient's global evaluation were as follows:

1) The famotidine 20 mg b.i.d. group was significantly better than the placebo in term of the distribution of the four assessment categories at weeks 2, 6 and 12 from both "all patients treated" and "per-protocol" analyses.

2) The famotidine 40 mg h.s. group was significantly better than the placebo for the distribution of the four assessment categories at weeks 2, 6 and 12 from the "all patients treated" analysis and at weeks 2 and 6 but not at week 12 from the "per protocol" analysis.

3) There were no significant differences between the famotidine 40 mg h.s. and the famotidine 20 mg b.i.d. groups from both "all patients treated" and "per protocol" analyses.

The sponsor also analyzed global evaluations by collapsing the four assessment categories into two: successful evaluation (moderate or excellent improvement) or unsuccessful evaluation (no or slight improvement). The results are given in Table 11. The results are similar to those based on the distribution of the four assessment categories in term of significance.

Thus, for this study there were consistent results in patient's global evaluation in favor of the famotidine 20 mg b.i.d. and 40 mg h.s. groups at weeks 2, 6, and 12. The results for famotidine 40 mg h.s. group are different in this study in comparison to study #009. The famotidine 40 mg h.s. group tends to be more effective, however, the results for the famotidine 40 mg h.s. is weaker than those for the famotidine 20 mg b.i.d.

2.1.2 Results for Complete Relief of Daytime Heartburn and Nighttime Heartburn

Relief/no relief data at the end of study was analyzed for daytime heartburn and nighttime heartburn using Fisher's Exact test. Patients with a baseline severity of none were included in the analyses as for study #009.

The results of completely relieved of daytime heartburn and nighttime heartburn symptoms by the end of study are given in Table 12. The results are summarized as follows:

1) Both famotidine groups were not significantly different from the placebo with respect to the proportion of patients completely relieved of daytime or nighttime heartburn symptoms by the end of study from both "all patients treated" and "per protocol" analyses. However, the famotidine 20 mg b.i.d. group was significantly better than the famotidine 40 mg h.s. group with respect to daytime heartburn from the "all patients treated" analysis but not from the "per protocol" analysis.

2) No significant difference of the proportion of patients completely relieved of nighttime heartburn symptoms by the end of study was observed among treatment groups from both "all patients treated" and "per protocol" analyses.

The time-to-complete symptom relief and no recurrence (score of 0) was assessed using the Mantel-Haenszel life-table methods, stratifying on average baseline score. Patients with no treatment period data or no baseline values were not included in the time-to-complete relief analysis.

The results of time to complete symptom relief are given in Table 13, As seen from Table 13, in both "all patients treated" and "per protocol" analyses, no significant treatment differences of time-to-complete daytime heartburn and nighttime heartburn relief were observed.

Hence, in this trial both famotidine groups were not significantly different from the placebo with respect to complete relief and time-to-relief for both daytime heartburn and nighttime heartburn symptoms.

2.2 Results for Secondary Efficay Variables

Secondary efficacy variables were esophagitis healing, complete relief of dysphagia and acid regurgitation, and antacid consumption.

2.2.1 Results for Esophagitis Healing

Approximately 71% of the patients enrolled had erosive esophagitis at baseline, and the percentage of patients with complete healing of erosive esophageal disease was evaluated at weeks 6 and 12. Table 14 gives the cumulative frequencies of healed esophagitis observed via endoscopy at

weeks 6 and 12 for erosive esophagitis patients. The healing rates were compared between any two of treatment groups using Mantel-Haenszel method. In this analysis, dropouts were considered as not healed. The results are summarized as follows:

Results for the Secondary Efficacy Variable
Favoring Famotidine 40 mg HS and 20 mg BID vs Placebo

Week 6

Comparison	All Patients Treated Healing Rate		2-tailed p-value	Per Protocol Healing Rate		2-tailed p-value
Fam 40 mg HS vs Placebo	28/98	(29%)	0.003	17/57	(30%)	0.066
	3/46	(7%)		2/21	(10%)	
Fam 20 mg BID vs Placebo	33/96	(34%)	< 0.001	23/65	(35%)	0.024
	3/46	(7%)		2/21	(10%)	

Week 12

Comparison	All Patients Treated Healing Rate		2-tailed p-value	Per Protocol Healing Rate		2-tailed p-value
Fam 40 mg HS vs Placebo	42/98	(43%)	0.053	26/57	(46%)	0.177
	12/46	(26%)		6/21	(29%)	
Fam 20 mg BID vs Placebo	48/96	(50%)	0.007	35/65	(54%)	0.045
	12/46	(26%)		6/21	(29%)	

The results for the secondary efficacy variable (# healed) were as follows:

1) The famotidine 20 mg b.i.d. group had significantly higher cumulative healing rates than the placebo at weeks 6 and 12 and after week 12 from both "all patients treated" and "per protocol" analyses.

2) The famotidine 40 mg h.s. group had significantly higher cumulative healing rates than the placebo at weeks 6 and 12 but not after week 12 from the "all patients treated" analysis. However, there was no significant difference observed in healing rates between the famotidine 40 mg h.s. group and the placebo group from the "per protocol" analysis.

3) No significant differences were observed between the two famotidine groups.

The sponsor also obtained the life table estimate of cumulative healing rates which are also presented in Table 15. This method assumed that dropouts healed at the same rate as those observed for patients who complete the study. The results are as follows:

1) The famotidine 20 mg b.i.d. group was significantly better than the placebo after week 12 from the "all patients treated" analysis but marginally better than the placebo from the "per protocol" analysis.

2) Famotidine 40 mg h.s. group was significantly better than the placebo after week 12 from the "all patients treated" analysis but not from the "per protocol" analysis.

3) No significant differences were observed between two famotidine groups.

Thus, there were consistent results in esophagitis healing for the famotidine 20 mg b.i.d. group after week 12. A stronger result by the "all patients treated" analysis was obtained, because, there were more dropouts in the placebo group than in the treatment groups and dropouts were considered unhealed.

2.2.2 Results for Other Secondary Efficacy Variables

Relief/no relief data at the end of study was also analyzed for dysphagia and acid regurgitation using Fisher's Exact test. The results are given in Table 13.

Average daily antacid consumption was calculated for each patients as the total number of antacid taken during the study divided by the total number of days the patient was in the study (cutoff at Day 84).

The results for secondary efficacy variables were as follows:

1) There were no treatment differences in term of the proportion of patients completely relieved of dysphagia and acid regurgitation from either "all patients treated" or "per protocol" analysis.

2) The famotidine 20 mg b.i.d. group used significantly less antacids than did the placebo group in term of median average daily antacid consumption (1.14 vs 1.99 $p<0.01$).

The most common clinical adverse experience in this study was abdominal pain.

3. Reviewer's Evaluation (Protocol #010)

3.1 Comments for Adjustment for Stratification

Sponsor's analyses of global evaluation and complete relief of symptoms

did not consider stratification of patients and differential study periods for two stratified subgroups of patients.

Eligible patients were stratified for the presence or absence of erosive esophagitis as demonstrated endoscopically and were randomized into the study. The treatment period was 6 to 12 weeks for erosive esophagitis patients and 6 weeks for non-erosive esophagitis patients.

Per this reviewer's request, the sponsor also performed analyses for global evaluation and relief/no relief adjusting for stratification. The adjusted and unadjusted analyses gave the same result in term of significance for this study.

3.2 Comments for Patient's Global Evaluation

In the sponsor's analyses, if a patient dropped out the study early, the last valid measurement was carried forward to subsequent timepoints. However, for the "per protocol" analysis of global evaluations, values were not carried forward in some specified cases. The determination of whether values were carried forward or not was made post-hoc. The values at week 6 were carried forward to week 12 for non-erosive esophagitis patients.

This reviewer reanalyzed global evaluation using Cochran-Mantel-Haenszel method to control for stratification. In this analysis, the values at week 6 were not carried forward to week 12 for non-erosive esophagitis patients. The week 12 analysis was based solely on erosive esophagitis patients. Results are given in Tables 16 and 17 for global evaluation and successful/unsuccessful global evaluation respectively. The results are similar to those given by the sponsor in term of significance at weeks 2 and 6 as seen in table below.

P-value for Analysis of Global Evaluation

(All Patients Treated)

	Sponsor's			Reviewer's		
	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC
Week 2	0.159	0.000	0.000	0.149	0.000	0.000
Week 6	0.063	0.000	0.000	0.060	0.000	0.000
Week 12	0.123	0.002	0.000	0.363	0.058	0.009

(Per Protocol)

	Sponsor's			Reviewer's		
	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC	FAM 40 vs FAM 20	FAM 40 vs PLC	FAM 20 vs PLC
Week 2	0.252	0.043	0.002	0.296	0.049	0.003
Week 6	0.127	0.037	0.001	0.140	0.041	0.001
Week 12	0.282	0.074	0.005	0.744	0.362	0.209

Hence, the famotidine 20 mg b.i.d. group was significantly better than the placebo in term of the distribution of the four assessment categories of global evaluation at weeks 2, 6 and 12 from "all patients treated" analysis and at weeks 2 and 6 but not at week 12 from the "per protocol" analysis. The famotidine 40 mg h.s. group was significantly better than the placebo in term of global evaluation at weeks 2, 6 and 12 from "all patients treated" analysis. But, the famotidine 40 mg h.s. group was marginally significantly better than the placebo at weeks 2 and 6 but not at week 12 from the "per protocol" analysis.

3.2 Comments for Esophagitis Healing

The cumulative healing rate was also analyzed by this reviewer using Fisher's Exact test for pairwise comparison and Mantel-Haenszel method for overall treatment comparison. The results are given in Table 14. The Fisher's Exact test produced p-values that are larger (less significant) than those reported by the sponsor. However, the results are similar to those reported by the sponsor in term of significance.

3.3 Comments for Antacid Consumption

As requested by this reviewer, the sponsor assessed the effect of antacid consumption on global assessment and heartburn relief. The average daily number of antacid tablets taken was calculated for each patient by dividing the total number of antacids taken during the study by the total number of days the patient was in the study. Each patient was then further classified into one of the following three categories:

Daily Number of Antacid Tablets taken = 0
Daily Number of Antacid Tablets greater than 0 and less than or equal to 2.
Daily Number of Antacid Tablets greater than 2

The analysis of global assessment and heartburn relief/no heartburn relief were then adjusted for these three levels of antacid consumption. When

adjusting for average daily antacid consumption, the overall significance were maintained.

However, it would be of interest to point out that for this study average daily antacid consumption has statistically significant ($P<0.05$) relationship to patients with global evaluation rating of moderate or excellent improvement and patients completely relieved of daytime heartburn and nighttime heartburn. That is, patients with moderate to excellent improvement in the global evaluation tend to use less antacid consumption than patients with "no" or "slight" improvement. Patients with completely relieved of daytime heartburn and nighttime heartburn tend to use less antacid than patients with no completely relieved of daytime heartburn and nighttime heartburn.

The analysis of esophagitis healing after week 12 were adjusted for these three levels of antacid consumption. The overall p-value adjusted for daily number of antacid tablets taken is much greater than the unadjusted p-value (2-sided p-value 0.098 vs 0.028). This appears to be due to slight imbalance across treatment groups with respect to daily number of antacid tablets taken (2-sided $p=0.105$).

This reviewer used Kruskal-Wallis test to compare the antacid consumption among treatment groups by week. The results revealed that significant difference was observed only at week 1. Thus, there was no significant difference of antacid consumption among treatments beyond week 1.

In summary, both studies #009 and #010 showed that there were consistent results in patient's global evaluation favoring famotidine 20 mg b.i.d. over placebo. Furthermore, study #009 showed that the famotidine 20 mg b.i.d. was significantly better than the famotidine 40 mg h.s. in term of the distribution of the four assessment categories of global evaluations but study #010 did not.

Study #009 also showed that there were consistent results favoring famotidine 20 mg b.i.d to placebo for relieving daytime heartburn. However, this result for study #009 was not replicated in study #010. Those disagreements might be due to different study populations. Study #009 consisted of only non-erosive esophagitis patients and study #010 consisted mostly of erosive esophagitis patients. In study #010, there were consistent results in esophagitis healing favoring famotidine 20 mg b.i.d. over placebo after 12 weeks.

D. Overall Summary and Recommendation

In support of the claim that the famotidine 20 mg b.i.d. is effective for the symptomatic treatment of patients with GERD, the sponsor has submitted two controlled clinical studies; protocol #009 and protocol #010.

Study #009 showed that the famotidine 20 mg b.i.d. was significantly better than the famotidine 40 mg h.s. in term of the distribution of the four assessment categories of global evaluations at weeks 2 and 6. The famotidine 20 mg b.i.d was superior to the placebo in term of the

distribution of the four assessment categories of global evaluations at both weeks 2 and 6 from the "all patient treated" analysis. But the "per protocol analysis" revealed that the famotidine 20 mg b.i.d. was only slightly significantly better than the placebo. The weaker results for the "per protocol" analysis is due to the fact that more patients with global evaluation scaling 2 or 3 dropped in the famotidine 20 mg b.i.d. and 40 mg h.s. groups as compared to the placebo group.

In study #009, there were consistent results favoring famotidine 20 mg b.i.d to placebo for relieving daytime heartburn.

Study #010 showed that there were consistent results in patient's global evaluation favoring famotidine 20 mg b.i.d. over placebo at weeks 2, 6, and 12. But, both famotidine 20 mg b.i.d. and 40 mg h.s. groups were not significantly different from the placebo with respect to complete relief and time-to-relief for daytime heartburn and nighttime heartburn.

In study #010, there were consistent results in esophagitis healing favoring famotidine 20 mg b.i.d. over placebo after 12 weeks. A stronger result by the "all patients treated" analysis was obtained, because, there were more dropouts in the placebo group than in the treatment groups and dropouts were considered unhealed.

Based on these two studies addressed in this review, following conclusion is drawn:

Famotidine 20 mg b.i.d. regimen was effective in both studies #009 and #010 in patient's global evaluation for the symptomatic treatment of patients with GERD. Famotidine 20 mg b.i.d. was effective in study #009 (but not in study #010) in relieving daytime heartburn after 6 weeks of treatment. In the second study #010, which included more severe patients than for study #009, the data indicated significant healing in favor of famotidine 20 b.i.d. group as compared to placebo.

E. Comments to be Conveyed to the Sponsor

The contents of Section E may be conveyed to the sponsor.

Milton C. Fan
Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 25 pages of text and 19 pages of tables.

concur: Dr. Huque Huque 10/2/91

Dr. Dubey 10-2-91

cc: Orig. NDA 19-462
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. DuBois
HFD-180/Mr. Hassall
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File:DRU 1.3.2 NDA]
HFD-713/Dr. Huque
HFD-713/Dr. Fan
Chron.
Dr. Fan/x7580/mcf/10/01/91

Table 1 Comparability of Treatment Groups at Baseline --- Protocol 009

Variable	Level	Famotidine 40 mg hs (n=155)	Famotidine 20 mg bid (n=158)	Placebo (n=76)	Fam 40 hs vs Fam 20 bid p-value	Fam 40 hs vs Placebo p-value	Fam 20 bid vs Placebo p-value	between treatment p-value
Age (mean)		44.2	45.3	44.5				
Sex	Male	74 (48%)	73 (46%)	45 (59%)			<0.10	0.159
	Female	81 (52%)	85 (54%)	31 (41%)				
Race	Caucasian	132 (85%)	135 (85%)	67 (88%)				0.517
	Negro	17 (11%)	21 (13%)	8 (11%)				
	Other	6 (4%)	2 (1%)	1 (1%)				
Smoking	No	108 (70%)	116 (73%)	49 (64%)				0.369
	Ye.	47 (30%)	42 (27%)	27 (36%)				
Alcohol	.o	140 (90%)	151 (96%)	68 (89%)	<0.10		<0.10	0.130
	Yes	15 (10%)	7 (4%)	8 (11%)				
Caffeine	No	41 (26%)	51 (32%)	23 (30%)				0.523
	Yes	114 (74%)	107 (68%)	53 (70%)				
History of Dysphagia	No	85 (55%)	101 (64%)	49 (64%)				0.187
	Yes	70 (45%)	57 (36%)	27 (36%)				
History of Acid Regurgitation	No	22 (14%)	21 (13%)	15 (20%)				0.410
	Yes	133 (86%)	137 (87%)	61 (80%)				
Esophagitis Grade	0	58 (37%)	62 (39%)	35 (46%)				0.443
	1	97 (63%)	96 (61%)	41 (54%)				
Abnormalities in Esophagus	No	121 (78%)	119 (75%)	66 (87%)			<0 10	0.128
	Yes	34 (22%)	39 (25%)	10 (13%)				
Abnormalities in Duodenum	No	138 (89%)	150 (95%)	69 (91%)	<0.10			0.155
	Yes	17 (11%)	8 (5%)	7 (9%)				
Daytime Heartburn	None	3 (2%)	3 (2%)	0 (0%)		<0.05		0.453
	Mild	61 (40%)	71 (45%)	32 (43%)				
	Moderate	86 (56%)	74 (47%)	34 (45%)				
	Severe	4 (3%)	8 (5%)	9 (12%)				
	Disabling	0 (0%)	2 (1%)	0 (0%)				
Nighttime Heartburn	None	28 (18%)	32 (20%)	14 (19%)	<0.05			0.903
	Mild	65 (42%)	65 (41%)	35 (47%)				
	Moderate	55 (36%)	47 (30%)	19 (25%)				
	Severe	5 (3%)	12 (8%)	7 (9%)				
	Disabling	0 (0%)	2 (1%)	0 (0%)				

P-values are 2-sided p-values.
Between treatment p-values were obtained by this reviewer

Table 2 Patient's Global Evaluation --- Protocol 009

(All Patients Treated)

week	treatment	no of patients	no improvment	slight improvment	moderate improvment	excellent improvment	vs 20 mg bid p-value	vs placebo p-value	overall p-value
2	FAM 40 mg hs	147	15 (10%)	49 (33%)	47 (32%)	36 (25%)	0.224	0.039	0.307
	FAM 20 mg bid	153	11 (7%)	35 (23%)	73 (46%)	34 (22%)		0.002	
	placebo	72	14 (19%)	22 (31%)	26 (36%)	10 (14%)			
6	FAM 40 mg hs	149	16 (11%)	31 (21%)	64 (43%)	38 (26%)	0.102	0.009	0.000
	FAM 20 mg bid	154	14 (9%)	14 (9%)	57 (37%)	69 (45%)		0.000	
	placebo	73	19 (26%)	9 (12%)	27 (37%)	18 (25%)			

(Per Protocol Analysis)

week	treatment	no of patients	no improvment	slight improvment	moderate improvment	excellent improvment	20 mg bid p-value	placebo p-value	overall p-value
2	FAM 40 mg hs	102	8 (8%)	32 (31%)	35 (34%)	27 (26%)	0.135	0.494	0.129
	FAM 20 mg bid	103	4 (4%)	20 (19%)	54 (52%)	25 (24%)		0.048	
	placebo	47	5 (11%)	14 (30%)	19 (40%)	9 (19%)			
6	FAM 40 mg hs	101	8 (8%)	20 (20%)	40 (40%)	33 (33%)	0.105	0.973	0.226
	FAM 20 mg bid	105	6 (6%)	9 (9%)	37 (35%)	53 (50%)		0.210	
	placebo	46	4 (9%)	6 (13%)	21 (46%)	15 (33%)			

P-values are 2-sided p-values.
P-values were obtained using Cochran-Mantel-Haenszel method.
Overall p-values were obtained by this reviewer.
Scales using were as follow:
0 - no improved
6 - slight improvement
7 - moderate improvement
9 - excellent improvement

Table 2 Patient's Global Evaluation --- Protocol 009

(All Patients Treated)

week	treatment	no of patients	no improvment	slight improvment	moderate improvment	excellent improvment	vs 20 mg bid p-value	vs placebo p-value	overall p-value
2	FAM 40 mg hs	147	15 (10%)	49 (33%)	47 (32%)	36 (25%)	0.224	0.059	0.007
	FAM 20 mg bid	153	11 (7%)	35 (23%)	73 (48%)	34 (22%)		0.002	
	placebo	72	14 (19%)	22 (31%)	26 (36%)	10 (14%)			
6	FAM 40 mg hs	149	16 (11%)	31 (21%)	64 (43%)	38 (26%)	0.102	0.009	0.000
	FAM 20 mg bid	154	14 (9%)	14 (9%)	57 (37%)	69 (45%)		0.000	
	placebo	73	19 (26%)	9 (12%)	27 (37%)	18 (25%)			

(Per Protocol Analysis)

week	treatment	no of patients	no improvment	slight improvment	moderate improvment	excellent improvment	20 mg bid p-value	placebo p-value	overall p-value
2	FAM 40 mg hs	102	8 (8%)	32 (31%)	35 (34%)	27 (26%)	0.135	0.494	0.129
	FAM 20 mg bid	103	4 (4%)	20 (19%)	54 (52%)	25 (24%)		0.048	
	placebo	47	5 (11%)	14 (30%)	19 (40%)	9 (19%)			
6	FAM 40 mg hs	101	8 (8%)	20 (20%)	40 (40%)	33 (33%)	0.105	0.973	0.226
	FAM 20 mg bid	105	6 (6%)	9 (9%)	37 (35%)	53 (50%)		0.210	
	placebo	46	4 (9%)	6 (13%)	21 (46%)	15 (33%)			

P-values are 2-sided p-values.
P-values were obtained using Cochran-Mantel-Haenszel method.
Overall p-values were obtained by this reviewer.
Scales using were as follow:
0 - no improved
6 - slight improvement
7 - moderate improvement
9 - excellent improvement

le 3 Analysis of Successful/Unsuccessful Global Evaluation -- Protocol 009

Analysis	Week	Treatment	No.	Succ. Rate	Comparison FAM 20 mg	p-value placebo	between treatment p-value
All Patients Treated	2	FAM 40 mg hs	147	83 (56%)	0.017	0.389	0.007
		FAM 20 mg bid	153	107 (70%)		0.005	
		Placebo	72	36 (50%)			
	6	FAM 40 mg hs	149	102 (68%)	0.008	0.365	0.002
		FAM 20 mg bid	154	126 (82%)		0.002	
		Placebo	73	45 (62%)			
Per Protocol	2	FAM 40 mg hs	102	62 (61%)	0.016	1.000	0.026
		FAM 20 mg bid	103	79 (77%)		0.051	
		Placebo	47	28 (60%)			
	6	FAM 40 mg hs	101	73 (72%)	0.025	0.544	0.061
		FAM 20 mg bid	105	90 (86%)		0.341	
		Placebo	46	36 (78%)			

P-values are 2-sided p-values.
Pairwsie p-values were obtained using Fisher's Exact test.
Overall p-values were obtained by this reviewer using Cochran-Mantel-
enszel method.

le 4 Sponsor's Analysis of Complete Relief --- Protocol 009

(All Patients Treated Analysis)

variable	treatment	N	Relief Rate	comparison Fam 20 mg	p-value placebo	between treatment p-value
Daytime Heartburn	Fam 40 mg HS	155	71 (46%)	0.018	0.323	0.004
	Fam 20 mg BID	158	94 (60%)		0.003	
	placebo	76	29 (38%)			
Nighttime Heartburn	Fam 40 mg HS	155	86 (56%)	0.028	0.779	0.031
	Fam 20 mg BID	158	107 (68%)		0.030	
	placebo	76	40 (53%)			
Dysphagia	Fam 40 mg HS	155	118 (76%)	0.588	1.000	0.795
	Fam 20 mg BID	158	125 (79%)		0.617	
	placebo	76	58 (76%)			
Acid Regurgitation	Fam 40 mg HS	155	101 (65%)	0.063	0.553	0.146
	Fam 20 mg BID	158	119 (75%)		0.429	
	placebo	76	53 (69%)			

(Per Protocol Analysis)

variable	treatment	N	Relief Rate	comparison Fam 20 mg	p-value placebo	between treatment p-value
Daytime Heartburn	Fam 40 mg HS	110	54 (49%)	0.004	0.502	0.002
	Fam 20 mg BID	198	74 (69%)		0.003	
	placebo	51	22 (43%)			
Nighttime Heartburn	Fam 40 mg HS	110	65 (59%)	0.032	0.730	0.084
	Fam 20 mg BID	108	79 (73%)		0.199	
	placebo	51	32 (63%)			
Dysphagia	Fam 40 mg HS	109	84 (77%)	0.229	1.000	0.389
	Fam 20 mg BID	108	91 (84%)		0.379	
	placebo	51	40 (78%)			
Acid Regurgitation	Fam 40 mg HS	109	77 (71%)	0.080	0.569	0.174
	Fam 20 mg BID	108	88 (82%)		0.526	
	placebo	51	39 (77%)			

P-values are 2-sided p-values.
Pairwise p-values were obtained using Fisher's Exact test.
Overall p-values were obtained using chi-square test.

.ble 5 Analysis of Successful/Unsuccessful Global Evaluation -- Protocol 009

Analysis	Variable	Meditan Time to Relief			FAM 40 hs vs FAM 20 bid p-value	FAM 40 hs vs placebo p-value	FAM 20 bid vs placebo p-value
		FAM 40 hs	FAM 20 bid	placebo			
All Patients Treated	Daytime Heartburn	>42.0	41.0	>42.0	0.01	0.66	0.02
	Nighttime Heartburn	42.0	40.0	>42.0	0.12	0.63	0.16
	Acid Regurgitation	39.0	37.0	39.0	0.38	0.23	0.81
	Dysphagia	16.5	18.5	7.0	0.34	0.86	0.64
Per Protocol	Daytime Heartburn	>42.0	40.0	>42.0	0.00	0.14	0.00
	Nighttime Heartburn	4' 0	38.5	42.0	0.03	0.57	0.07
	Acid Regurgitation	38.0	35.0	37.0	0.26	0.57	0.66
	Dysphagia	16.0	13.0	8.0	0.41	0.95	0.65

P-values are two-sided p-values.
-values were obtained using uncoorected CMH statistics controlled for baseline scores.

Table 6 Reviewer's Analysis of Patient's Global Evaluation --- Protocol 009

(All Patients Treated)

							Cochran-Mantel-Haenszel			Nonparametric		
							vs	vs		vs	vs	
week	treatment	no.	no improvement	slight improvement	moderate improvement	excellent improvement	20 mg bid p-value	placebo p-value	overall p-value	20 mg bid p-value	placebo p-value	overall p-value
2	FAM 40 mg hs	147	15 (10%)	49 (33%)	47 (32%)	36 (25%)	0.172	0.057	0.009	0.164	0.075	0.012
	FAM 20 mg bid	153	11 (7%)	35 (23%)	73 (48%)	34 (22%)		0.002			0.003	
	placebo	72	14 (19%)	22 (31%)	26 (36%)	10 (14%)						
6	FAM 40 mg hs	149	16 (11%)	31 (21%)	64 (43%)	38 (26%)	0.020	0.110	0.000	0.000	0.016	0.000
	FAM 20 mg bid	154	14 (9%)	14 (9%)	57 (37%)	69 (45%)		0.000			0.000	
	placebo	73	19 (26%)	9 (12%)	27 (37%)	18 (25%)						

(Per Protocol Analysis)

							Cochran-Mantel-Haenszel			Nonparametric		
							vs	vs		vs	vs	
week	treatment	no.	no improvement	slight improvement	moderate improvement	excellent improvement	20 mg bid p-value	placebo p-value	overall p-value	20 mg bid p-value	placebo p-value	overall p-value
2	FAM 40 mg hs	102	8 (8%)	32 (31%)	35 (34%)	27 (26%)	0.139	0.485	0.122	0.161	0.516	0.142
	FAM 20 mg bid	103	4 (4%)	20 (19%)	54 (52%)	25 (24%)		0.046			0.060	
	placebo	47	5 (11%)	14 (30%)	19 (40%)	9 (19%)						
6	FAM 40 mg hs	101	8 (8%)	20 (20%)	40 (40%)	33 (33%)	0.105	0.973	0.276	0.004	0.736	0.011
	FAM 20 mg bid	105	6 (6%)	9 (9%)	37 (35%)	53 (50%)		0.210			0.045	
	placebo	46	4 (9%)	6 (13%)	21 (46%)	15 (33%)						

P-values are 2-sided p-values.
P-values were obtained using Cochran-Mantel-Haenszel method.
Overall p-values were obtained by this reviewer.
scales using were as follow:
0 - no improved
1 - slight improvement
2 - moderate improvement
3 - excellent improvement

ble 7 Reviewer's Analysis of Patient's Global Evaluation at Week 6 (No Forward) --- Protocol 009

							Cochran-Mantel-Haenszel Method		
							vs	vs	
analysis	treatment	no.	no improvment	slight improvment	moderate improvment	excellent improvment	20 mg bid p-value	placebo p-value	overall p-value
All Patient Treated	FAM 40 mg hs	134	10 (7%)	26 (19%)	62 (46%)	36 (27%)	0.015	0.312	0.006
	FAM 20 mg bid	150	13 (9%)	13 (9%)	57 (38%)	67 (45%)		0.006	
	placebo	64	12 (19%)	8 (13%)	26 (41%)	18 (28%)			
Per Protocol	FAM 40 mg hs	95	6 (6%)	20 (21%)	38 (40%)	31 (33%)	0.017	0.628	0.047
	FAM 20 mg bid	103	6 (6%)	9 (9%)	37 (36%)	51 (50%)		0.146	
	placebo	45	3 (7%)	6 (13%)	21 (47%)	15 (33%)			

P-values are two-sided p-values.
p-values are 2-sided p-values.

: 8 Reviewer's Analysis of Complete Relief --- Protocol 009

(All Patients Treated Analysis)

variable	treatment	N	Relief Rate	comparison p-value Fam 20 mg	placebo	between treatment p-value
Daytime Heartburn	Fam 40 mg HS	145	68 (47%)	0.027	0.315	0.006
	Fam 20 mg BID	151	91 (60%)		0.004	
	placebo	74	29 (39%)			
Nighttime Heartburn	Fam 40 mg HS	120	71 (59%)	0.186	0.156	0.033
	Fam 20 mg BID	123	83 (67%)		0.011	
	placebo	61	29 (48%)			
Dysphagia	Fam 40 mg HS	52	26 (50%)	0.697	0.795	0.785
	Fam 20 mg BID	50	27 (54%)		0.599	
	placebo	20	9 (45%)			
Acid Regurgitation	Fam 40 mg HS	92	51 (55%)	0.054	0.593	0.138
	Fam 20 mg BID	101	70 (69%)		0.359	
	placebo	49	30 (61%)			

(Per Protocol Analysis)

variable	treatment	N	Relief Rate	comparison p-value Fam 20 mg	placebo	between treatment p-value
Daytime Heartburn	Fam 40 mg HS	96	54 (56%)	0.078	0.168	0.009
	Fam 20 mg BID	104	72 (69%)		0.004	
	placebo	50	22 (44%)			
Nighttime Heartburn	Fam 40 mg HS	84	51 (61%)	0.104	0.705	0.126
	Fam 20 mg BID	85	62 (73%)		0.106	
	placebo	42	24 (57%)			
Dysphagia	Fam 40 mg HS	38	19 (50%)	0.458	1.000	0.660
	Fam 20 mg BID	28	17 (61%)		0.530	
	placebo	14	7 (50%)			
Acid Regurgitation	Fam 40 mg HS	64	42 (66%)	0.174	1.000	0.274
	Fam 20 mg BID	67	52 (78%)		0.332	
	placebo	33	22 (67%)			

P-values are 2-sided.
Pairwise p-values were obtained using Fisher's Exact test.
Overall p-value was obtained using chi-square test.
:ents with no baseline score or with no treatment score
with missing data were excluded in these analyses.

Table 9 Comparability of Treatment Groups at Baseline
Protocol 010

Variable	Level	Famotidine 40 mg hs (n=135)	Famotidine 20 mg bid (n=137)	Placebo (n=66)	between treatment p-value
Age (mean)		47.9	47.3	46.9	
Sex	Male	79 (59%)	74 (54%)	39 (59%)	0.693
	Female	56 (41%)	63 (46%)	27 (41%)	
Race	Caucasian	102 (76%)	104 (76%)	51 (77%)	0.711
	Negro	10 (7%)	9 (7%)	3 (5%)	
	Hispanic	21 (16%)	23 (17%)	12 (18%)	
	Other	2 (1%)	1 (1%)	0 (0%)	
Smoking	No	105 (78%)	103 (75%)	51 (77%)	0.872
	Yes	30 (22%)	34 (25%)	15 (23%)	
Alcohol	No	114 (84%)	113 (82%)	58 (88%)	0.612
	Yes	21 (16%)	24 (18%)	8 (12%)	
Caffeine	No	41 (30%)	45 (33%)	24 (36%)	0.693
	Yes	94 (70%)	92 (67%)	42 (64%)	
History of Nocturnal Pyrosis	No	71 (53%)	74 (54%)	42 (64%)	0.310
	Yes	64 (47%)	63 (46%)	24 (36%)	
History of Acid Regurgitation	No	17 (13%)	18 (13%)	6 (9%)	0.695
	Yes	118 (87%)	119 (87%)	60 (91%)	
Esophagitis Grade	0	25 (19%)	28 (20%)	15 (23%)	0.823
	1	12 (9%)	13 (9%)	5 (8%)	
	2	35 (26%)	37 (27%)	16 (24%)	
	3	53 (39%)	50 (36%)	25 (38%)	
	4	10 (7%)	9 (7%)	5 (8%)	
Abnormalities in Esophagus	No	92 (69%)	89 (65%)	42 (65%)	0.892
	Yes	41 (31%)	47 (35%)	23 (35%)	
Abnormalities in Duodenum	No	115 (86%)	119 (87%)	55 (83%)	0.591
	Yes	19 (14%)	18 (13%)	11 (17%)	
Daytime Heartburn	None	2 (1%)	1 (1%)	2 (3%)	0.382
	Mild	20 (15%)	29 (21%)	15 (23%)	
	Moderate	65 (48%)	63 (46%)	28 (43%)	
	Severe	44 (33%)	39 (29%)	18 (28%)	
	Disabling	4 (3%)	4 (3%)	2 (3%)	
Nighttime Heartburn	None	10 (7%)	12 (9%)	5 (8%)	0.893
	Mild	30 (22%)	28 (21%)	13 (20%)	
	Moderate	43 (32%)	46 (34%)	19 (29%)	
	Severe	46 (34%)	41 (30%)	25 (38%)	
	Disabling	6 (4%)	9 (7%)	3 (5%)	

P-values are 2-sided p-values.

10 Patient's Global Evaluation --- Protocol 010

(All Patients Treated)

week	treatment	no of patients	no improvment	slight improvment	moderate improvment	excellent improvment	20 mg bid p-value	vs placebo p-value	overall p-value
2	FAM 40 mg hs	129	20 (16%)	35 (27%)	53 (41%)	21 (16%)	0.159	0.000	0.000
	FAM 20 mg bid	131	11 (8%)	38 (29%)	56 (43%)	26 (20%)		0.000	
	placebo	62	21 (34%)	27 (44%)	11 (18%)	3 (5%)			
6	FAM 40 mg hs	129	19 (15%)	27 (21%)	51 (40%)	32 (25%)	0.063	0.000	0.000
	FAM 20 mg bid	131	9 (7%)	26 (20%)	57 (44%)	39 (30%)		0.000	
	placebo	62	20 (32%)	18 (29%)	17 (27%)	7 (11%)			
12	FAM 40 mg hs	129	18 (14%)	26 (20%)	45 (35%)	40 (31%)	0.123	0.002	0.000
	FAM 20 mg bid	131	10 (8%)	23 (18%)	53 (40%)	45 (34%)		0.000	
	placebo	62	19 (31%)	14 (23%)	19 (31%)	10 (16%)			

(Per Protocol Analysis)

week	treatment	no of patients	no improvment	slight improvment	moderate improvment	excellent improvment	20 mg bid p-value	placebo p-value	overall p-value
2	FAM 40 mg hs	83	11 (13%)	22 (27%)	35 (42%)	15 (18%)	0.252	0.043	0.013
	FAM 20 mg bid	87	5 (6%)	24 (28%)	41 (47%)	17 (20%)		0.002	
	placebo	31	5 (16%)	16 (52%)	7 (23%)	3 (10%)			
6	FAM 40 mg hs	83	10 (12%)	17 (20%)	33 (40%)	23 (28%)	0.127	0.037	0.004
	FAM 20 mg bid	86	4 (5%)	17 (20%)	36 (42%)	29 (34%)		0.001	
	placebo	31	7 (23%)	11 (35%)	7 (23%)	6 (19%)			
12	FAM 40 mg hs	79	10 (13%)	14 (18%)	26 (33%)	29 (37%)	0.282	0.074	0.025
	FAM 20 mg bid	86	4 (5%)	14 (17%)	36 (43%)	30 (36%)		0.005	
	placebo	31	6 (20%)	9 (30%)	8 (27%)	7 (23%)			

P-values are 2-sided p-values.
P-values were obtained using Cochran-Mantel-Haenszel method.

Table 11 Analysis of Successful/Unsuccessful Global Evaluation -- Protocol 010

Analysis	Week	Treatment	No.	Succ. Rate	Comparison FAM 20 mg	p-value placebo	between treatment p-value
All Patients Treated	2	FAM 40 mg hs	129	74 (57%)	0.448	0.000	0.000
		FAM 20 mg bid	131	82 (63%)		0.000	
		Placebo	62	14 (23%)			
	6	FAM 40 mg hs	129	83 (64%)	0.141	0.001	0.000
		FAM 20 mg bid	131	96 (73%)		0.000	
		Placebo	62	24 (39%)			
	12	FAM 40 mg hs	129	85 (66%)	0.135	0.018	0.001
		FAM 20 mg bid	131	98 (75%)		0.000	
		Placebo	62	29 (47%)			
Per Protocol	2	FAM 40 mg hs	83	50 (60%)	0.427	0.011	0.004
		FAM 20 mg bid	87	58 (67%)		0.001	
		Placebo	31	10 (33%)			
	6	FAM 40 mg hs	83	56 (67%)	0.306	0.018	0.003
		FAM 20 mg bid	86	65 (76%)		0.002	
		Placebo	31	13 (42%)			
	12	FAM 40 mg hs	79	55 (70%)	0.213	0.074	0.013
		FAM 20 mg bid	86	66 (79%)		0.005	
		Placebo	30	15 (50%)			

P-values are 2-sided p-values.
Pairwsie p-values were obtained using Fisher's Exact test.
Overall p-values were obtained by this reviewer using Cochran-Mantel-Haenszel method.

Table 12 Sponsor's Analysis of Complete Relief --- Protocol 011

(All Patients Treated Analysis)

variable	treatment	N	Relief Rate	comparison p-value Fam 20 mg	placebo	between treatment p-value
Daytime Heartburn	Fam 40 mg HS	135	57 (42%)	0.022	0.762	0.060
	Fam 20 mg BID	137	77 (56%)		0.177	
	placebo	66	30 (46%)			
Nighttime Heartburn	Fam 40 mg HS	135	68 (50%)	0.274	0.881	0.349
	Fam 20 mg BID	137	79 (58%)		0.232	
	placebo	66	32 (49%)			
Dysphagia	Fam 40 mg HS	135	96 (71%)	0.268	0.738	0.499
	Fam 20 mg BID	137	106 (77%)		0.725	
	placebo	66	49 (74%)			
Acid Regurgitation	Fam 40 mg HS	135	75 (56%)	0.082	0.545	0.186
	Fam 20 mg BID	137	91 (66%)		0.437	
	placebo	66	40 (61%)			

(Per Protocol Analysis)

variable	treatment	N	Relief Rate	comparison p-value Fam 20 mg	placebo	between treatment p-value
Daytime Heartburn	Fam 40 mg HS	86	41 (48%)	0.133	0.544	0.291
	Fam 20 mg BID	91	54 (59%)		0.839	
	placebo	34	19 (56%)			
Nighttime Heartburn	Fam 40 mg HS	86	48 (56%)	0.651	0.682	0.809
	Fam 20 mg BID	91	54 (59%)		0.840	
	placebo	34	21 (62%)			
Dysphagia	Fam 40 mg HS	86	65 (76%)	0.367	1.000	0.631
	Fam 20 mg BID	91	74 (81%)		0.617	
	placebo	34	26 (77%)			
Acid Regurgitation	Fam 40 mg HS	86	49 (57%)	0.119	0.309	0.212
	Fam 20 mg BID	91	63 (69%)		1.000	
	placebo	34	23 (68%)			

P-values are 2-sided p-values.
Pairwise p-values were obtained by this reviewer using Fisher's Exact test.
Overall p-values were obtained by this reviewer using chi-square test.
This table was tabulated by this reviewer.

e 13 Mantel-Haenszel Comparison of Survival Curve of Time to Relif --- Protocol 010

Analysis	Variable	Median Time to Relief (Days) FAM 40 hs	FAM 20 bid	placebo	FAM 40 hs vs FAM 20 bid p-value	FAM 40 hs vs placebo p-value	FAM 20 bid vs placebo p-value
All Patients Treated	Daytime Heartburn	>84.0	83.0	>84.0	0.12	0.72	0.08
	Nighttime Heartburn	>84.0	74.0	>84.0	0.28	0.42	0.17
	Acid Regurgitation	79.0	44.5	77.0	0.07	0.40	0.29
	Dysphagia	39.0	21.5	31.0	0.45	0.63	0.13
Per Protocol	Daytime Heartburn	>84.0	82.0	80.0	0.23	0.61	0.57
	Nighttime Heartburn	80.0	78.0	79.0	0.44	0.76	0.70
	Acid Regurgitation	79.0	48.0	69.0	0.04	0.20	0.41
	Dysphagia	31.0	10.0	40.0	0.64	0.38	0.11

P-values were obtained from the uncorrected Cochran-Haenszel statistics contolled for
eline scores.

Table 14 Cumulative Cude Rate of Esophagitis Healing --- Protocol 010

Analysis	Week	Treatment	No.	Healing Rate	sponsor's reported comparison p-values FAM 20 bid	sponsor's reported comparison p-values Placebo	reviewer's comparison p-values FAM 20 bid	reviewer's comparison p-values Placebo
All Patients Treated	6	FAM 40 hs	98	28 (29%)	0.385	0.003	0.440	0.002
		FAM 20 bid	96	33 (34%)		<0.001		0.000
		Placebo	46	3 (7%)				
	12	FAM 40 hs	98	42 (43%)	0.320	0.053	0.388	0.065
		FAM 20 bid	9	48 (50%)		0.007		0.011
		Placebo	46	12 (26%)				
	after 12	FAM 40 hs	98	43 (44%)	0.254	0.074	0.314	0.099
		FAM 20 bid	96	50 (52%)		0.008		0.011
		Placebo	46	13 (28%)				
Per Protocol	6	FAM 40 hs	57	17 (30%)	0.516	0.066	0.565	0.079
		FAM 20 bid	65	23 (35%)		0.024		0.027
		Placebo	21	2 (10%)				
	12	FAM 40 hs	57	26 (46%)	0.366	0.177	0.468	0.204
		FAM 20 bid	65	35 (54%)		0.045		0.049
		Placebo	21	6 (29%)				
	after 12	FAM 40 hs	57	27 (47%)	0.379	0.139	0.468	0.197
		FAM 20 bid	65	36 (66%)		0.034		0.045
		Placebo	21	6 (29%)				

P-values are 2-sided p-values.
Reviewer's pairwise p-values were obtained using Fisher's Exact test.
Between treatment p-values were obtained using Cochran-Mantel-Haenszel method.

Table 15 Cumulative Life Table Rate of Esophagitis Healing --- Protocol 010

Analysis	Week	Treatment	Rate	sponsor's reported comparison p-values FAM 20 bid	Placebo
All Patients Treated	6	FAM 40 hs	28.6%	n.a.	<0.05
		FAM 20 bid	24.4%		<0.05
		Placebo	6.5%		
	12	FAM 40 hs	49.8%	n.a.	<0.05
		FAM 20 bid	54.5%		<0.05
		Placebo	36.6%		
	after 12	FAM 40 hs	51.4%	0.383	0.041
		FAM 20 bid	57.1%		0.007
		Placebo	33.9%		
Per Protocol	6	FAM 40 hs	n.a.	n.a.	n.a.
		FAM 20 bid	n.a.		n.a.
		Placebo	n.a.		
	12	FAM 40 hs	n.a.	n.a.	n.a.
		FAM 20 bid	n.a.		n.a.
		Placebo	n.a.		
	after 12	FAM 40 hs	54.0%	0.448	0.173
		FAM 20 bid	60.8%		0.059
		Placebo	42.4%		

P-values are 2-sided p-values.
P-values were Mantel- Haenszel uncorrected p-values.
n.a. denotes "not available; the sponsor did not give the value"

: 16 Reviewer's Analysis of Patient's Global Evaluation --- Protocol 010

(All Patients Treated)

week	group	treatment	no of patients	no improvement	slight improvement	moderate improvement	excellent improvement	vs 20 mg bid p-value	vs placebo p-value	overall p-value
2	Erosive	FAM 40 mg hs	93	11 (12%)	27 (29%)	38 (41%)	17 (18%)	0.495	0.000	0.000
		FAM 20 mg bid	91	8 (9%)	27 (30%)	36 (40%)	20 (22%)		0.000	
		placebo	43	11 (26%)	23 (53%)	9 (21%)	0 (0%)			
	Nonerosive	FAM 40 mg hs	36	9 (25%)	8 (22%)	15 (42%)	4 (11%)	0.109	0.102	0.011
		FAM 20 mg bid	40	3 (8%)	11 (28%)	20 (50%)	6 (15%)		0.003	
		placebo	19	10 (53%)	4 (21%)	2 (11%)	3 (16%)			
	Total	FAM 40 mg hs	129	20 (16%)	35 (27%)	53 (41%)	21 (16%)	0.149	0.000	0.000
		FAM 20 mg bid	131	11 (8%)	38 (29%)	56 (43%)	26 (20%)		0.000	
		placebo	62	21 (34%)	27 (44%)	11 (18%)	3 (5%)			
6	Erosive	FAM 40 mg hs	93	12 (13%)	17 (18%)	42 (45%)	22 (24%)	0.213	0.014	0.002
		FAM 20 mg bid	91	7 (8%)	18 (20%)	37 (41%)	29 (32%)		0.001	
		placebo	43	10 (23%)	14 (33%)	13 (30%)	6 (14%)			
	Nonerosive	FAM 40 mg hs	36	7 (19%)	10 (28%)	9 (25%)	10 (28%)	0.128	0.010	0.000
		FAM 20 mg bid	40	2 (5%)	8 (20%)	20 (50%)	10 (25%)		0.000	
		placebo	19	10 (53%)	4 (21%)	4 (21%)	1 (5%)			
	Total	FAM 40 mg hs	129	19 (15%)	27 (21%)	51 (40%)	32 (25%)	0.060	0.000	0.000
		FAM 20 mg bid	131	9 (7%)	26 (20%)	57 (44%)	39 (30%)		0.000	
		placebo	62	20 (32%)	18 (29%)	17 (27%)	7 (11%)			
12		FAM 40 mg hs	93	11 (12%)	16 (17%)	36 (39%)	30 (32%)	0.363	0.058	0.031
		FAM 20 mg bid	91	8 (9%)	15 (16%)	33 (36%)	35 (38%)		0.009	
		placebo	43	9 (21%)	10 (23%)	15 (35%)	9 (21%)			

P-values are 2-sided p-values.
P-values were obtained using Cochran-Mantel-Haenszel method.
P-values for total were controlled for stratification.
0 - no improved
1 - slight improvement
2 - moderate improvement
3 - excellent improvement

Table 16 Reviewer's Analysis of Patient's Global Evaluation --- Protocol 010 (Continued)

(Per Protocol)

week	group	treatment	no of patients	no improvment	slight improvment	moderate improvment	excellent improvment	vs 20 mg bid p-value	vs placebo p-value	overall p-value
2	Erosive	FAM 40 mg hs	54	3 (6%)	16 (30%)	23 (43%)	12 (22%)	0.392	0.003	0.006
		FAM 20 mg bid	61	3 (5%)	18 (30%)	26 (43%)	14 (23%)		0.002	
		placebo	19	2 (11%)	12 (63%)	5 (26%)	0 (0%)			
	Nonerosive	FAM 40 mg hs	29	8 (28%)	6 (21%)	12 (41%)	3 (10%)	0.120	0.841	0.309
		FAM 20 mg bid	26	2 (8%)	6 (23%)	15 (58%)	3 (12%)		0.324	
		placebo	12	3 (25%)	4 (33%)	2 (17%)	3 (25%)			
	Total	FAM 40 mg hs	83	11 (13%)	22 (27%)	35 (42%)	15 (18%)	0.296	0.049	0.017
		FAM 20 mg bid	87	5 (6%)	24 (28%)	41 (47%)	17 (20%)		0.003	
		placebo	31	5 (16%)	16 (52%)	7 (23%)	3 (10%)			
6	Erosive	FAM 40 mg hs	54	5 (9%)	10 (19%)	24 (44%)	15 (28%)	0.344	0.194	0.129
		FAM 20 mg bid	60	3 (5%)	12 (20%)	23 (38%)	22 (37%)		0.047	
		placebo	19	2 (11%)	9 (47%)	3 (16%)	5 (26%)			
	Nonerosive	FAM 40 mg hs	29	5 (17%)	7 (24%)	9 (31%)	8 (28%)	0.230	0.108	0.035
		FAM 20 mg bid	26	1 (4%)	5 (19%)	13 (50%)	7 (27%)		0.008	
		placebo	12	5 (42%)	2 (17%)	4 (33%)	1 (8%)			
	Total	FAM 40 mg hs	83	10 (12%)	17 (20%)	33 (40%)	23 (28%)	0.140	0.041	0.006
		FAM 20 mg bid	86	4 (5%)	17 (20%)	36 (42%)	29 (34%)		0.001	
		placebo	31	7 (23%)	11 (35%)	7 (23%)	6 (19%)			
12		FAM 40 mg hs	50	5 (10%)	7 (14%)	17 (34%)	21 (42%)	0.744	0.362	0.295
		FAM 20 mg bid	58	3 (5%)	9 (16%)	23 (40%)	23 (40%)		0.209	
		placebo	18	1 (6%)	7 (39%)	4 (22%)	6 (33%)			

P-values are 2-sided p-values.
P-values were obtained using Cochran-Mantel-Haenszel method.
P-values for total were controlled for stratification.
0 - no improved
1 - slight improvement
2 - moderate improvement
3 - excellent improvement

Table 17 Reviewer's Analysis of Successful/Unsuccessful Global Evaluation
--- Protocol 010

(All Patients Treated)

Week	Group	Treatment	No.	Succ. Rate	Comparison FAM 20 mg	p-value placebo	between treatment p-value
2	Erosive	FAM 40 mg hs	93	55 (59%)	0.765	0.000	0.000
		FAM 20 mg bid	91	56 (62%)		0.000	
		Placebo	43	9 (21%)			
	Nonerosive	FAM 40 mg hs	36	19 (53%)	0.352	0.087	0.022
		FAM 20 mg bid	40	26 (65%)		0.011	
		Placebo	19	5 (26%)			
	Total	FAM 40 mg hs	129	74 (57%)	0.388	0.000	0.000
		FAM 20 mg bid	131	82 (63%)		0.000	
		Placebo	62	14 (23%)			
6	Erosive	FAM 40 mg hs	93	64 (69%)	0.629	0.008	0.004
		FAM 20 mg bid	91	66 (73%)		0.002	
		Placebo	43	19 (44%)			
	Nonerosive	FAM 40 mg hs	36	19 (53%)	0.056	0.087	0.002
		FAM 20 mg bid	40	30 (75%)		0.001	
		Placebo	19	5 (26%)			
	Total	FAM 40 mg hs	129	83 (64%)	0.114	0.001	0.000
		FAM 20 mg bid	131	96 (73%)		0.000	
		Placebo	62	24 (39%)			
12	Erosive	FAM 40 mg hs	93	66 (71%)	0.621	0.118	0.080
		FAM 20 mg bid	91	68 (75%)		0.001	
		Placebo	43	24 (56%)			

P-values are 2-sided p-values.
Pairwise p-values were obtained using Fisher's Exact test.
Overall p-values were obtained using Cochran-Mantel-Haenszel method.

Table 17 Reviewer's Analysis of Successful/Unsuccessful Global Evaluation
--- Protocol 010 (Continued)

(Per Protocol)

Week	Group	Treatment	No.	Succ. Rate	Comparison FAM 20 mg	p-value placebo	between treatment p-value
2	Erosive	FAM 40 mg hs	54	35 (65%)	1.000	0.007	0.006
		FAM 20 mg bid	61	40 (66%)		0.004	
		Placebo	19	5 (26%)			
	Nonerosive	FAM 40 mg hs	29	15 (52%)	0.271	0.734	0.222
		FAM 20 mg bid	26	18 (69%)		0.157	
		Placebo	12	5 (42%)			
	Total	FAM 40 mg hs	83	50 (60%)	0.406	0.009	0.004
		FAM 20 mg bid	87	58 (67%)		0.001	
		Placebo	31	10 (33%)			
6	Erosive	FAM 40 mg hs	54	39 (72%)	0.832	0.026	0.022
		FAM 20 mg bid	60	45 (75%)		0.012	
		Placebo	19	8 (42%)			
	Nonerosive	FAM 40 mg hs	29	17 (59%)	0.166	0.493	0.098
		FAM 20 mg bid	26	20 (77%)		0.064	
		Placebo	12	5 (42%)			
	Total	FAM 40 mg hs	83	56 (67%)	0.262	0.015	0.004
		FAM 20 mg bid	86	65 (76%)		0.001	
		Placebo	31	13 (42%)			
12	Erosive	FAM 40 mg hs	50	38 (76%)	0.817	0.134	0.126
		FAM 20 mg bid	58	46 (79%)		0.066	
		Placebo	18	10 (56%)			

P-values are 2-sided p-values.
Pairwise p-values were obtained using Fisher's Exact test.
Overall p-values were obtained using Cochran-Mantel-Haensze' method.