CLINICAL REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S EFFICACY REVIEW

NDA:	**20-325/S-015**
Sponsor:	**Merck & Co., Inc. BLX-29, P.O. Box 4 West Point, PA 19486**
Date Submitted:	**November 2002**
Drug Name:	**Famotidine (Pepcid) Oral Tablet**
Drug Class:	**H_2-Receptor Antagonist**
Proposed Indication:	**Prevention and Treatment of Intermittent Heartburn**
Documents Reviewed:	**Clinical Section of the NDA Volumes 1-3 (Electronic and Paper Submission) Pepcid 20 mg Package Insert**
Division Director:	**Robert Justice, M.D., M.S.**
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Clinical Efficacy Review for NDA 20-325/S-015

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Based on my efficacy evaluation, the studies (P114, P117 and P128) reviewed in this submission support the approval of Pepcid 20 mg tablet for the *prevention* of meal induced heartburn, and studies (P017 and 019) support the approval of Pepcid 20 mg tablet for *treatment* of episodic heartburn. For safety assessment, please see the Division of Over-the-Counter (OTC) Medical Officer's Review.

The prevention studies showed that famotidine 20 mg is consistently superior to placebo. The studies also demonstrated numeric trend and statistical evidence favoring famotidine 20mg to the 10 mg dose. The treatment studies has also shown that famotidine 20 mg is significantly effective in relieving heartburn as measured by the patients' global assessment of efficacy and heartburn relief within one hour of dosing. There was also a numeric trend favoring famotidine 20 mg to the 10 mg dose.

Therefore, from a clinical efficacy standpoint, this reviewer recommends over-the-counter use of famotidine 20 mg for prevention and treatment of *episodic* heartburn.

For final recommendation on approvability, please see the Division of OTC recommendation.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There is no recommendation for Phase IV commitments or Risk Management based on my efficacy assessment.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Pepcid (famotidine) is an H_2-receptor antagonist which has been approved in the United States since October, 1986 for the treatment of a variety of acid-related gastrointestinal disorders. This drug binds to the parietal cell H_2-receptor and competitively inhibits histamine-stimulated gastric acid secretion, thereby raising intragastric pH. It is currently available by prescription as 20-mg and 40-mg tablets, orally disintegrating tablets; oral suspension (40 mg/5 mL); and parenteral formulations. It is also available as a 10 mg OTC product for the relief and prevention of heartburn and sour stomach.

In this submission, the sponsor seeks approval for marketing famotidine 20 mg for over the counter use for prevention and treatment of meal induced heartburn. For prevention indication, a total of 3357 adult patients were enrolled in 3 clinical trials in the United States. The studies were multicenter, randomized, double-blind, comparing famotidine 20mg, famotidine 10 mg and placebo in preventing heartburn symptoms when administered 10 minutes prior to a provocative meal.

To support the treatment indication, the data from the original NDA 20-325 treatment studies (017 & 019) were used. In these trials, a total of 850 patients were enrolled in a double-blind, multicenter, dose ranging, parallel design, placebo-controlled studies conducted in the United States. The study drug treatments were famotidine 20mg, famotidine 10mg, famotidine 5mg (017 only), antacid and placebo. These studies were previously reviewed for the approval of famotidine 10mg for OTC use.

B. Efficacy

Three prevention studies (P114, P117, and P128) were reviewed to evaluate the efficacy of famotidine 10 mg and 20 mg in preventing meal induced heartburn. The primary endpoint for all 3 prevention trials was similar. The two treatment trials (P017 and 019) which were included in the original NDA for PEPCID™ AC (NDA 20-325) to support a treatment of heartburn indication for OTC famotidine 10 mg were presented to demonstrate the efficacy of famotidine 20 mg in the relief of spontaneously occurring intermittent heartburn. All patients who participated in the study were adults of ≥18 years old and with heartburn episodes of at least 3x a week. The studies were conducted in two phases: the baseline phase and the double blind phase.

For the indication of prevention of heartburn:

The prevention studies were all conducted in-clinic, single-dose, double-blind, randomized, double-dummy, placebo-controlled, multicenter, parallel-design studies with 3 treatment groups: famotidine 20 mg, famotidine 10 mg, and placebo. The primary endpoint was peak heartburn severity during the 3-hour period following a provocative meal and the secondary endpoints were: (1) the proportion of patients with no heartburn during the 3 hours following the start of the meal, (2) mean heartburn severity during the 3 hours following the start of the meal, (3) global assessment of efficacy measured at the end of the treatment period (all categories) and (4) proportion of patients reporting good/ very good/ global assessment. Studies P114 and P117 also evaluated proportion of patients reporting no awakenings with heartburn; in addition, Study P117 evaluated proportion of patients who used rescue medications.

The 3 studies enrolled similar populations into the *baseline phase*: a history of food-induced heartburn of at least 2 months duration, with at least 3 episodes per week. In Study P114, patients were included if they have moderate to severe heartburn by history, and had to develop severe heartburn after an in-clinic ingestion of a provocative meal. In Study P117 and P128, patients completed a 1-week at-home baseline period to verify heartburn frequency and severity. Patients identified specific foods and beverages that produced symptoms and used antacids and/or OTC H2RAs for effective relief of their symptoms. During the *double-blind phase*, patients received study medication 10 minutes prior to consuming a provocative meal then assessed the presence of heartburn symptoms at 30-minute intervals beginning 30 minutes after the start of the meal and continuing for 3 hours. Heartburn severity was rated using a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). Patients received a take-home diary in which to record any rescue antacid use, awakenings with heartburn, and a global evaluation.

For peak heartburn severity, the proportion of patients reporting "mild" and "none" during the 3 hours postmeal tabulated by study is shown below.

Table 1
Proportion of patients reporting "Mild" and "None" during the 3 hours postmeal tabulated by study is shown below.

Study	Famotidine 20 mg (cum%)	Famotidine 10 mg (cum%)	Placebo (cum%)
P114	36.4*@	28.8	22.1
P117	69.9*#	61.28	49.8
P128	72.3*@	68.5	61.0

Reviewer's table
* p-value<0.001 compared to placebo
# p-value<0.002 compared to famotidine 10 mg
@ p-value<0.06 compared to famotidine 10 mg

All three studies demonstrated that famotidine 20 mg was superior to placebo with p-value <0.001. Study P117 has shown that famotidine 20mg was statistically better than famotidine 10 mg (p<0.002), studies P114 and P128 are numerically supportive but only showed borderline statistical significance.

Table 2
Proportion of Patients Reporting Complete Prevention (No Heartburn)
During the 3 Hours Postmeal

Study	Famotidine 20 mg % (n/N)	Famotidine 10 mg % (n/N)	Placebo % (n/N)
P114	10.7 (28/261)*+	7.7 (21/271)	4.2 (11/262)
P117	37.9 (185/1227)*#	30 (147/1227)	18.9 (47/1227)
P128	41.2 (219/1332)*@	35.4 (190/1332)	26.9 (71/1332)

Reviewer's table

* p<0.004 compared to placebo
+ p<0.241 compared to 10 mg
@ p<0.047 compared to 10 mg
# p<0.006 compared to 10 mg

The percentage of patients reporting complete prevention of heartburn varies from 10.7% to 41.2%. The difference between famotidine 20 mg and placebo is consistently significant in the three studies. Studies P117 and P128 prove that famotidine 20 mg is better than 10 mg for complete prevention of heartburn during the 3 hours postmeal.

In summary, the 3 prevention studies (P114, P117 & P128) have shown that famotidine 20 mg is consistently and significantly more effective than placebo in preventing meal induced heartburn with p<0.01 for all efficacy endpoint outcomes. In addition, famotidine 20 mg was significantly more effective than famotidine 10 mg as evidenced by the proportion of patients reporting no heartburn (Study P117, p=0.006 and Study P128, p=0.047), and peak heartburn severity during the 3 hours postmeal (Study P117, p=0.002), supported by Study P128, with a marginal statistical significance but favorable numerical trend. Famotidine 10 mg is also significantly superior than placebo in preventing heartburn (Studies P117 and P128). In general, these studies have shown a statistical and numerical trend, favoring the 20 mg dose to the 10 mg dose in preventing meal induced heartburn.

Patients in the famotidine 20mg group compared to the 10 mg group did not show consistent significant statistical difference with regard to the global assessment of efficacy measured at the end of the treatment period (all categories), proportion of patients reporting good/ very good/ global assessment and, no awakenings with heartburn.

For the indication of treatment of heartburn:

Treatment studies (P017 and 019) were conducted as multidose, double-blind, randomized, double-dummy, placebo-controlled, multicenter, parallel, at-home

treatment of heartburn trials. The treatment groups were famotidine 20 mg, famotidine 10 mg, 5 mg (for P017), antacid, and placebo.

In the baseline phase, patients with a history of heartburn requiring self-medication with antacid 3 or more times a week participated in a 1-week, single-blind, at-home evaluation were enrolled. Patients who qualified for entry into the double-blind phase were randomized to 1 of 5 arms (4 for P019). At hourly intervals following dosing for treatment of heartburn, patients recorded (in the diary card) whether their heartburn was Completely Relieved, Better, Unchanged, or Worse, as compared to the severity of heartburn at the time of dosing. Rescue antacid was also provided if the medications were not effective.

The primary endpoints of the studies were response to therapy and global assessment of efficacy. The data was analyzed to determine if the treatment groups differ with respect to the (1) number of episodes requiring self-medication occurring during the 4-week study (2) patients global evaluation of the test drug upon completion of the study (3) time onset of heartburn relief (looking specifically at a patient's first episode) (4) proportion of episodes completely relieved of heartburn symptoms (5) proportion of episodes requiring antacid rescue medication (6) proportion of episodes requiring re-medication.

Table 3

Complete Relief Within 1 Hour of Dosing (Protocol 017, N=552)

Treatment Group	N	Total Heartburn Episodes	Model-Adjusted Probability of Complete Relief Within 1 Hour
Famotidine 20 mg*#	113	2664	0.379
Famotidine 10 mg@	109	2642	0.344
Famotidine 5 mg	110	2612	0.307
Antacid	112	2559	0.296
Placebo	108	2534	0.235

* $p<0.001$ compared to placebo # $p<0.40$ compared to 10 mg

@ $p<0.004$ compared to placebo

Table 4

Complete Relief Within 1 Hour of Dosing (Protocol 019, N=500)

Treatment Group	N	Total Heartburn Episodes	Model-Adjusted Probability of Complete Relief Within 1 Hour
Famotidine 20 mg*#	129	2512	0.362
Famotidine 10 mg*	122	2362	0.325
Antacid	121	2456	0.301
Placebo	128	2619	0.217

* $p<0.001$ compared to placebo # $p<0.325$ compared to 10 mg

Both treatment studies P017 and P019 demonstrated that famotidine 20 mg was better than placebo when patients globally assessed their response to treatment and when proportion of heartburn episodes completely relieved within *1 hour* dosing was assessed ($p<0.001$ for both studies).

Study P017 demonstrated that when patients reported the proportion of heartburn episodes relieved, famotidine 20mg was significantly superior to placebo ($p=0.001$), antacid ($p=0.0382$) and famotidine 5 mg ($p=0.0224$); there was no statistical difference between the 20 mg and 10 mg dose. This is in contrast to the results of Study P019, in which famotidine 20 mg did not show any difference with placebo ($p=0.351$), antacid ($p=0.372$), and famotidine 10 mg ($p=0.431$).

With regard to the proportion of heartburn episodes requiring back-up medication, in study P017, all of the famotidine and antacid treatment groups had a lower proportion of heartburn episodes requiring back-up medication compared to the placebo group (with a p-value ranging form 0.001 to 0.003). There was no significant statistical difference among the active treatment groups. There was numerically a higher proportion of heartburn episodes (22%) in the famotidine 20mg group that did not require back-up medication, compared to famotidine 10 mg (16%), 5 mg (13%)antacid (16%), and placebo (14%).

In assessing the proportion of heartburn episodes requiring no re-medication, study P017 showed that only famotidine 10 mg was significantly better than placebo ($p=0.0048$), all treatment groups showed numerically more favorable results than placebo. Sixty-nine percent (69%) of the episodes in the famotidine 20mg group, 76% in the famotidine 10 mg group, 67% in the famotidine 5 mg group, 66% in the antacid group, compared to 59% in the placebo group, required no re-medication.

None of the studies showed significant statistical evidence that famotidine 20 mg or 10 mg was better over the other treatment groups in requiring back-up medication and re-medication. Famotidine 20 mg showed some numerically favorable results when assessing episodes requiring re-medication and no back-up medication.

C. **Safety** (See Division of Over-the-Counter Products Review on Safety)

D. Dosing

Dose: Famotidine 20mg oral tablet for OTC use

Indication: Prevention and treatment of episodic heartburn, acid indigestion and sour stomach.

Regimen: Prevention: 1 tablet 15 to 60 minutes before eating food or drinking beverages that cause heartburn.
Do not take more than 2 tablets in 24 hours.

Treatment: 1 tablet up to twice a day.

Stop use and see a doctor if you need to take this product for more than 14 days.

The proposed famotidine 20 mg dose is twice as high than the presently approved OTC 10mg dose. Prevention study P117 has shown that Famotidine 20 mg taken 10 minutes prior to a provocative meal is more effective than famotidine 10mg in preventing episodes of heartburn. Studies P114 and P128 are supportive of this indication. Treatment studies 017 and 019 have shown that there is an evidence of a numerical trend favoring the famotidine 20mg dose with respect to the proportion of heartburn episodes relieved, although the difference between the famotidine 20mg and 10mg dose did not reach a statistical significance. Famotidine 20mg has been used for over 16 years with ——— prescriptions dispensed for oral formulations in the U.S. from 1993 to 2001.

Dosage adjustment is necessary in patients with moderate to severe renal impairment. The package insert addresses the use of famotidine in patients with moderate to severe renal insufficiency. The elimination half-life of famotidine is increased in these patients and may exceed 20 hours; CNS adverse events have been reported. Therefore, to avoid excess accumulation of the drug, the dose maybe reduced to half or the dosing interval maybe prolonged to 36-48 hours as indicated by the patient's clinical response.

For safety evaluation and recommendation of dosage adjustment, please see OTC Medical Officer's Safety Review.

The treatment for overdosage is symptomatic and supportive, unabsorbed material should be removed from the gastrointestinal tract. Oral dosages of up to 640 mg/day have been given to adult patients with pathological hypersecretory conditions with no serious adverse effects. This is addressed in the prescription package insert. The proposed 20mg is acceptable for OTC use.

E. Special Populations

In the prevention studies, a total of 3357 were enrolled; majority of patients were Caucasians (75%), middle aged, and with more females than males (65% vs. 35%). In the treatment studies, there were a total of 1050 patients; majority of the patients are Caucasians (88%), middle aged and with balanced female to male ratio. The studied population was appropriate for the studies conducted.

Gender
There was no significant gender differences found in the effectiveness of this drug.

Race
For the treatment studies, it appears that there was no evidence of a treatment-by-race interaction with patients classified as Caucasian or non-Caucasian for the patients in the treatment studies. The treatment effects were consistent for both of these race groups.

For prevention, Study P114, with *Caucasians=554 patients (70%) and non-Caucasians=240 patients (30%); of these non-Caucasians, 180 (75%) are black* and Study P117 with *Caucasians=930 patients (76%) and non-Caucasians=299 patients (24%); of these non-Caucasians, 195 (65%) are black*), efficacy was consistent across race groups. However, for Study P128, (*Caucasians=1063 patients (80%) and non-Caucasians=271 patients (20%); of these non-Caucasians, 236 (87%) are black,* the test for treatment-by-race interaction was significant (p=0.006); the active treatment groups had more favorable responses than the placebo group for the Caucasian patients, the response of the non-Caucasian (Black, Hispanic, and "other" groups) was the opposite. It appears that the interpretation of this finding is confounded by the potential differences in response by site as the majority (76%) of the non-Caucasian patients were enrolled at 6 of the 15 investigator sites. This finding is unlikely to have been responsible for the absence of a statistically significant difference in the primary endpoint.

Pediatrics
Pediatric patients were not evaluated, only patients who are 18 years or older were evaluated in this NDA, although the indication is from age 12 years and older. As reflected in the current famotidine 20 mg label, in patients 1 to 15 years of age, doses of 0.5 mg/kg were associated with a mean area under the curve (AUC) similar to that seen in adults treated with 40 mg. Limited published studies suggest a starting dose also suggest that the relationship between serum concentration and acid suppression is similar in pediatric patients 1-15 years compared to adults. Therefore, the proposed population for 12 years and older is acceptable.

The applicant did not propose OTC use of this drug in children less than 12 years old. This drug should only be given to children < 12 years old who are under the supervision of a physician if given as over-the-counter.

Geriatrics
Efficacy of this drug was consistent across age groups. The were only a total of 32 (N=1050) patients in the treatment studies and 94 (N=3357) in the prevention

studies who were more than 65 years old, and who received famotidine 20 mg, a population too small to permit analysis of that demographic subgroup.

This submission did not reveal any issues particular to the geriatric population. The risk of toxic reactions to this drug maybe greater in patients with impaired renal function. The current prescription label states that no dosage adjustment is required based on age, however, because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. For safety evaluation, please see OTC Medical Officer's Safety Review.

Pregnancy

Pregnant women were excluded in this NDA. Famotidine is currently listed as Pregnancy Category B. There are no adequate or well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This application has no new information regarding pregnant women.

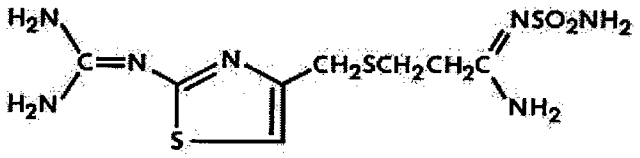
Nursing Mothers

Famotidine is detectable in human 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. Because of the potential for serious adverse reactions in nursing infants, this drug should only be used if the potential benefit justifies the potential risk to the infant. This is reflected in the current package insert and on the proposed OTC label.

Clinical Review

I. Introduction and Background

A. Drug: Pepcid 20 mg (Famotidine) Tablets



Class: H_2 - receptor antagonist
Proposed Indication(s): Prevention and treatment of episodic heartburn, acid indigestion and sour stomach

Regimen: Prevention: 1 tablet 15 to 60 minutes before eating food or drinking beverages that cause heartburn.
Do not take more than 2 tablets in 24 hours.

Treatment: 1 tablet up to twice a day.

If this product needs to be used for more than 14 days, consult a physician.

Age Groups: Adults, and children 12 years and older.

B. State of Armamentarium for Indication(s)

There are four H_2-receptor antagonists (famotidine, cimetidine, ranitidine and nizatidine) approved for use in the United States. Currently, famotidine, cimetidine, ranitidine are being used for heartburn and acid-related gastrointestinal disorders and are all available for OTC use at a lower strength dosage (half the prescription strength). The applicant is proposing for the OTC use of prescription strength famotidine 20mg.

C. Important Milestones in Product Development

Pepcid was approved by the FDA in October, 1986 for the treatment of a variety of acid-related gastrointestinal disorders including active duodenal and acute benign gastric ulcer. It is also approved for the treatment of pathological hypersecretory conditions, e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas. On December 10, 1991, it was approved for the treatment of gastritis, acute symptomatic and erosive gastroesophageal reflux disease (GERD). On April 30, 1995, Pepcid AC ("Acid Controller") 10 mg became available for OTC use for the relief and prevention of heartburn, acid indigestion and sour stomach.

PEPCID™ is currently available by prescription as 20-mg and 40-mg tablets, orally disintegrating tablets, oral suspension (40 mg/5 mL), and parenteral formulations.

On November 22, 2002, Merck Research Laboratories (MRL) submitted Supplement 015 (S-015) to the original Famotidine (Pepcid) NDA 20-325. This supplement seeks the approval of a 20 mg strength nonprescription famotidine tablet. The sponsor submitted prevention studies to support that the 20 mg strength provides more effective and rapid relief of existing heartburn and more complete prevention than the currently available famotidine 10 mg OTC product. Treatment studies (017 and 019) from the original NDA 20-325 were used to support treatment indication.

In one of the pre-NDA meetings held between the Agency and the sponsor, it was agreed that approvability would not require demonstration of a statistically significant difference between famotidine 20 mg and 10 mg, but rather a demonstration of a dose response with a "clinically meaningful" difference.

D. Other Relevant Information

Famotidine is marketed in 68 countries worldwide. As of 26-Aug-2002, the marketing approval or application of famotidine has not been rejected, suspended, revoked, or withdrawn by agency in any country. Pepcid 10 mg chewable tablets has been withdrawn due to [redacted] in 3 countries (Finland, Norway and Sweden).

E. Important Issues with Pharmacologically Related Agents

It is known that cimetidine is more likely than others to provoke interactions with hepatically metabolized drugs. Famotidine is less likely than cimetidine to interact with other drugs.

Some clinicians believe that this drug class cause adverse CNS effects but retrospective literature could not identify one H_2-receptor antagonist as being more likely than the others to cause this reaction. CNS reactions are more likely to occur in elderly patients and/or those with renal impairment.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

For this NDA supplement, there is no change in the formulation or route of administration. No new animal or toxicology studies were submitted and microbiology studies are not applicable for this drug class.

Dr. Milton Fan from biometrics conducted the statistical review.

In the current present package insert report, animal studies showed no evidence of carcinogenic potential for famotidine. In rat studies, fertility and reproductive performance were not affected and there were no direct fetotoxic effects observed. However, sporadic abortions occurred at oral doses of 250 times the usual human dose or higher in some rabbits displaying marked decrease in food intake.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

For human pK information, please see FDA's Biopharm Review of NDA 20-325 and prescription package insert of this product.

B. Pharmacodynamics

Study RefP118, which is included in this submission, characterized the pharmacodynamic profile of famotidine 20-mg film-coated tablet (FCT), famotidine 10-mg FCT, and placebo. Esophageal and gastric pH were both measured to define and compare the relative antisecretory action of famotidine 10- and 20-mg doses. This study demonstrated that Famotidine 20 mg produces a higher gastric pH (lower acidity) than famotidine 10 mg and placebo as measured by mean area under the intragastric pH/time curve and the percentage of time when intragastric pH is >3.0 during the 1.5- to 13.5-hour postdose period. In addition, famotidine 20 mg produces a higher gastric pH than famotidine 10 mg and placebo as measured by the mean area under the intragastric pH/time curve during the 4- to 12-hour postdose nocturnal period when patients are reclining in bed. Both of these differences also achieved statistical significance.

IV. Description of Clinical Data and Sources

A. Overall Data

Clinical Section of the NDA Volumes 1-3 paper copy and electronic submission
Data and Reviews from Studies 017 and 019 from the Original NDA 20-325
Package Insert: Famotidine 20 mg
Pharmacology Online
Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 9th ed.
Orange Book

B. Tables Listing the Clinical Trials

Table 5
Clinical Trials and Indications in Support of NDA 20-325, S015

Study	Title	Indication	# of Patients
P114	Multicenter Study: Randomized, Single-Dose Study Comparing Famotidine 20 mg, 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered 10 Minutes Prior to a Provocative Meal	Prevention	794
P117	Multicenter Study: Randomized, Single-Dose, Double-Blind, Parallel Study Comparing Famotidine 20 mg, 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered 10 Minutes Prior to a Provocative Meal	Prevention	1229
P128	Multicenter Study: An In-Clinic, Randomized, Single-Dose, Double-Blind, Parallel Study Comparing Famotidine 20 mg, 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered Prior to a Provocative Meal	Prevention	1334
P137	A Randomized, Double-Blind, Multidose, Pilot Study Comparing the Efficacy of Famotidine 20 mg and Placebo in Preventing Heartburn and Acid Reflux When Administered Immediately Prior to a Provocative Meal (*Pilot Study*)	Prevention	287
P017	Multicenter Study: A Double-Blind, Dose Ranging Study to Evaluate the Effects of Doses as Needed up to Twice Daily of Famotidine 5 mg, 10 mg, 20 mg, or Antacid, as Compared to Placebo in the Treatment of Intermittent Heartburn	Treatment	552
P019	Multicenter Study: A Double-Blind, Dose Ranging Study to Evaluate the Effects of Famotidine 10 mg, 20 mg, or Antacid, as Compared to Placebo as Needed up to Twice Daily in the Treatment of Intermittent Heartburn	Treatment	498
P118	A Double-Blind, Three-Period, Crossover Study to Compare the Effect of Famotidine 20 mg,10 mg, and Placebo on Gastric and Esophageal pH Profiles in Patients Who Experience Heartburn	Pharmacody-namics	24

These studies were all conducted in the United States.

C. Postmarketing Experience

It is estimated that 186 million patients had used OTC famotidine in the United States through June, 2002; and [redacted] prescriptions for oral formulations had been dispensed in the United States from 1993 through 2001.

A review of the Adverse Experience Reports received by the sponsor for patients treated with oral formulations of famotidine shows that the percentage of adverse experiences are similar for the various dosage formulations.

D. Literature Review

The applicant submitted multiple references/articles from peer reviewed journal, a bibliography of published clinical literature, a report from toxic exposure surveillance system (TESS) and a summary of adverse event data from Merck Worldwide Adverse Experience System (WAES).

V. Clinical Review Methods

A. How the Review was Conducted

The applicant's proposal for the OTC use of Famotidine 20mg was based on 3 pivotal prevention studies submitted with this application, and the 2 treatment studies submitted with the original NDA 20-325. A multispecialty review was done by physicians, statisticians, chemists, and a project manager.

This NDA was submitted to the Division of Over-the-Counter Drug Products, and Division of Gastrointestinal Drug Products is consulted for the Efficacy Review.

B. Overview of Materials Consulted in Review

Clinical Section of sNDA (S-015) Volumes 1-3 printed material
Electronic Submission on a CD-ROM, with Studies 017 and 019 included
Package insert: Pepcid 20 mg tablets
Physicians' Desk Reference Online
Pharmacology Online
Orange Book
Medline
Basic and Clinical Pharmacology-8th Ed., Bertram Katzung, Lange/McGraw Hill
Goodman and Gilman's Pharmacological Basis of Therapeutics, 9th Ed., Pergamon Press
Medical Officer's Review of NDA 20-325 (submission used for approval of OTC Famotidine 10 mg)
Medical Officer's Review of NDA 19-462 (submission used for approval of Famotidine 20 mg for gastroesophageal reflux disease indication)

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A comprehensive review of the 3 prevention and 2 treatment studies was performed with periodic sampling of case reports. There was no discrepancy between the case report forms and the data submitted. The quality and results of the data was discussed in consultation with the Agency's Biostatistics Department. The Office of Compliance reported that the EER (establishment evaluation report) was acceptable based on profile.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All studies submitted in this NDA were conducted in accordance with the Declaration of Helsinki and in accordance with Good Clinical Practice.

E. Evaluation of Financial Disclosure

The applicant submitted an FDA Form 3454 certifying that none of the investigators of the covered clinical studies had any financial interests to disclose.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The three pivotal studies submitted for prevention indication (Studies P114, P117 and 128) demonstrated consistently the efficacy of famotidine 20 mg for the prevention of heartburn when taken 10 minutes prior to a provocative meal as compared to placebo; $p \leq 0.01$ for all efficacy endpoint outcomes for the three studies. Studies P117 and P128 demonstrated that famotidine 10mg was better than placebo, with a $p \leq 0.05$ for all efficacy endpoints for both of these studies.

In addition, famotidine 20 mg was more effective than famotidine 10 mg in preventing heartburn, as measured by the peak heartburn severity (primary efficacy parameter) and the proportion of patients reporting no heartburn symptoms during 3 hours postmeal (secondary efficacy parameter). In reporting peak heartburn severity, Study P117 demonstrated significant statistical difference favoring the 20 mg to the 10 mg dose ($p \leq 0.01$), this is supported by Study P128 which numerically favorable difference but only marginal statistical significance ($p=0.066$).

With regard to the proportion of patients reporting no heartburn during 3 hours postmeal, famotidine 20mg was significantly better than famotidine 10 mg as demonstrated in Studies P117 ($p=0.006$) and P128 ($p=0.047$).

Patients in the famotidine 20mg group, compared to the 10 mg group did not show consistent significant statistical difference with regard to the global assessment of efficacy measured at the end of the treatment period (all categories), proportion of patients reporting good/ very good/ global assessment and ,no awakenings with heartburn.

To support treatment indication for acute heartburn, the data from the original NDA 20-325 treatment studies (017 & 019) were utilized by the applicant. These studies were previously reviewed for the approval of famotidine 10mg for OTC use. These studies have shown that famotidine 20 mg was more effective in completely relieving episodes of heartburn within the first hour as compared to placebo ($p<0.001$ for both studies); and although not statistically significant, both studies show some numerical trend favoring famotidine 20 mg when compared to the 10 mg dose. This numerical difference is clinically relevant given the high prevalence of heartburn in the population.

B. General Approach to Review of the Efficacy of the Drug

Efficacy was assessed by utilizing the data submitted by the applicant comprising three prevention studies, and two treatment studies (data from the original NDA 20-325). Studies were reviewed and compared for efficacy results. Statistical analysis were reviewed in consultation with the biometrics review team. Summaries, supporting tables and case reports were consulted as needed.

This reviewer also utilized the Medical Officer's Review of supplement NDA 19-462 which was submitted to support the treatment of erosions, ulcerations and heartburn associated with gastroesophageal reflux disease.

C. Detailed Review of Trials by Indication

A full summary and review of each of the prevention trials is included in the appendix.

Prevention:
Study P114: See Appendix A
Study P117: See Appendix B
Study P128: See Appendix C

Treatment:
Study P017: See Appendix D
Study P019: See Appendix E

Prevention

Three pivotal studies Reference P114, P117 and P128 were conducted to evaluate the safety and efficacy of famotidine 20 mg and 10 mg in preventing meal induced heartburn. These studies were all conducted in the United States and multicenter, randomized, single-dose, comparing famotidine 20 mg, famotidine 10 mg and placebo in preventing heartburn symptoms when administered 10 minutes prior to a provocative meal. The baseline features across treatment groups were well-balanced. The primary efficacy parameter for these studies was peak heartburn during 3 hours postmeal. The secondary parameters similar to the 3 studies were: (1) proportion of patients reporting no heartburn and (2) mean heartburn severity during 3 hours postmeal, (3) global assessment of efficacy measured at the end of treatment period (all categories), and (4) proportion of patients reporting good/very good/excellent global assessment.

There were some differences among the studies for the secondary parameters. Study P117 and P114 determined the proportion of patients reporting no awakenings with heartburn, and P117 determined the proportion of patients using rescue medication during the study. Another difference among the studies is the entry criteria; Study P114 enrolled patients with severe heartburn during a screening meal, while Studies P117 and P128 enrolled patients with ≥3 heartburn episodes during a one-week baseline run-in period, of which 30% should be severe. See table below.

Table 6

Prevention			
Study	***Entry Criteria***	***Secondary Parameters***	
P114	***Severe heartburn during screening meal***	**- proportion of patients reporting no heartburn during 3 hours postmeal** **- mean heartburn severity during 3 hours postmeal** **- global assessment of efficacy measured at the end of treatment period (all categories)** **- proportion of patients reporting good/ very good/ excellent global assessment**	**-proportion of patients reporting no awakenings with heartburn**
P117	**≥3 heartburn episodes during baseline period, with ≥ 30% severe**	**- same as above**	**-proportion of patients reporting no awakenings with heartburn** ***-proportion of patients using rescue medication during the study***
P128	**Same as P117**	**- same as above**	

The data from all three prevention studies have successfully demonstrated that famotidine 20 mg is consistently and significantly more effective than placebo in preventing meal induced heartburn. Famotidine 10 mg is also significantly better than placebo. In addition, famotidine 20 mg was significantly more effective than famotidine 10 mg with regards to the proportion of patients reporting no heartburn during the 3 hours postmeal; and in reporting peak heartburn severity, famotidine 20 mg was more effective than 10 mg as demonstrated by the results from Study

P117 which showed statistical significance and supported by Study P128, although this only showed borderline statistical significance.

Patients in the famotidine 20mg group compared to the 10 mg group did not show consistent significant statistical difference with regard to the global assessment of efficacy measured at the end of the treatment period (all categories), proportion of patients reporting good/ very good/ global assessment and no awakenings with heartburn.

In general, these studies have shown a numerical trend, favoring the 20 mg dose to the 10 mg dose in preventing meal induced heartburn. In terms of baseline demographics, the treatment groups were well balanced.

Treatment

Two studies from the original NDA 20-325 reviewed for the approval of Famotidine 10 mg for OTC use were submitted to support treatment indication. These studies were conducted comparing the safety and efficacy of famotidine 20 mg, 10 mg, 5 mg (P019 only), antacid and placebo. All were conducted in the United States, multicenter, randomized, double-blind, parallel, placebo-controlled, at-home, multiple-episode treatment of heartburn trial.

The primary endpoints of the studies were response to therapy and global assessment of efficacy. The data was analyzed to determine if the treatment groups differ with respect to the (1) number of episodes requiring self-medication occurring during the 4-week study (2) patients global evaluation of the test drug upon completion of the study (3) time onset of heartburn relief (looking specifically at a patient's first episode) (4) proportion of episodes completely relieved of heartburn symptoms (5) proportion of episodes requiring antacid rescue medication (6) proportion of episodes requiring re-medication.
In study P017, there were more males than females (54% vs. 46%), and 80% of the patients had daily heartburn episodes; while in study P019, there were more females than males (53% vs. 47%) and 70% of the patients had daily heartburn episodes. The baseline features of patients were reasonably well balanced across treatment groups.

The study plan for these two studies were essentially the same except for some differences tabulated below:

Table 7
Differences in Study Plan for P017 vs. P019

P017	P019
Famotidine 5 mg used	Not used
Required to wait 3 hours between doses	Required to wait 5 hours between doses
Did not indicate if meals or drink precipitate episode	Indicated
Baseline phase, record response at 1,2, & 3 hours after dosing	Record response at 1,2,3,4, & 5 hours after dosing
Double-blind phase record response to therapy at ½ ,1, 1-½, 2, & 3 hrs. after 1st double-blind dose and at 1, 2, & 3 hours after all other double-blind doses	Double-blind phase record response to therapy at ¼, ½ ,1, 1-½, 2, 3, 4 & 5 hrs. after 1st double-blind dose and at 1, 2, 3, 4, & 5 hours after all other double-blind doses
Not required to record exact time and date for all back-up medications	Required
Upper gastrointestinal endoscopy and motility studies done	Not done

Both treatment studies P017 and P019 demonstrated that famotidine 20 mg was better than placebo when patients globally assessed their response to treatment. In addition, for study P017, famotidine 20 mg was also better than the 10 mg dose. In study 019, famotidine 20mg was better than placebo using the ITT analysis, however, all famotidine doses were better than placebo using PPA.

Study P017 demonstrated that with regard to the proportion of heartburn episodes relieved, famotidine 20mg was significantly superior to placebo, antacid and famotidine 5 mg; this is in contrast to the results of Study P019, which showed no significant difference among the treatment groups.

For both studies, when proportion of heartburn episodes completely relieved within *1 hour* dosing was assessed, both famotidine 20 mg and 10 mg were significantly superior to placebo. In addition, patients who took famotidine 20 mg appear to have a numerically greater probability of complete heartburn relief and more likely to report complete relief compared to those on famotidine 10 mg and placebo.

None of the studies showed significant evidence that famotidine 20 mg or 10 mg was better over the other treatment groups in requiring back-up medication and re-medication. Famotidine 20 mg showed some numerically favorable results when assessing episodes requiring re-medication and no back-up medications. Approximately 80% of patients used back-up medication for at least one heartburn episode during these trials.

D. Efficacy Conclusions

In summary, the three pivotal prevention studies (P114, P117 & P128) submitted by the applicant demonstrated that famotidine 20 mg is consistently and significantly more effective than placebo in preventing meal induced heartburn. This is proven by all the statistical endpoint outcomes. In addition, famotidine 20 mg was significantly more effective than famotidine 10 mg as evidenced by the proportion of patients reporting no heartburn and peak heartburn severity during the 3 hours postmeal.

Patients in the famotidine 20mg group compared to the 10 mg group did not show consistent significant statistical difference with regard to the global assessment of efficacy measured at the end of the treatment period (all categories), proportion of patients reporting good/ very good/ global assessment and, no awakenings with heartburn.

Famotidine 10 mg is also significantly superior than placebo in preventing heartburn. In general, these studies have shown a numerical trend, favoring the 20 mg dose to the 10 mg dose in preventing meal induced heartburn.

Both treatment studies (P017 & P019) demonstrated that famotidine 20 mg was better than placebo when patients globally assessed their response to treatment; and when the proportion of heartburn episodes completely relieved within *1 hour* dosing was assessed, both famotidine 20 mg and 10 mg were significantly superior to placebo. In addition, patients who took famotidine 20 mg appear to have a numerically greater probability of complete heartburn relief and more likely to report complete relief compared to those on famotidine 10 mg and placebo.

VII. Integrated Review of Safety

(See Division of Other the Counter Drugs for Safety Review)

VIII. Dosing, Regimen, and Administration Issues

Proposed Indications: Prevention and treatment of:

- heartburn
- acid indigestion
- sour stomach

Dose: 1 Pepcid AC 20 mg film coated tablet up to twice a day

Administration:

- To relieve symptoms (Prevention): swallow 1 tablet with a glass of water (do not chew).
- To prevent symptoms (Treatment): swallow 1 tablet with a glass of water anytime from *15 to 60 minutes* before eating food or drinking beverages that cause heartburn.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

It did not appear that there was a difference on efficacy based on gender for all studies.There were more females than males in the three prevention studies (60% vs. 40%) and slightly more of males than females (50 vs. 55%) in the treatment studies. The treatment effects were consistent for both males and females.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

For all patients in these studies, efficacy was consistent across age groups. The were only a total of 32 (N=1050) patients in the treatment studies and 94 (N=3357) in the prevention studies who were more than 65 years old, and who received famotidine 20 mg, a population too small to permit analysis of that demographic subgroup.

It appears that there was no evidence of a treatment-by-race interaction with patients classified as Caucasian or non-Caucasian for the patients in the treatment studies. The treatment effects were consistent for both of these race groups.

For prevention, Study P114, with *Caucasians=554 patients (70%) and non-Caucasians=240 patients (30%); of these non-Caucasians, 180 (75%) are black* and Study P117 with *Caucasians=930 patients (76%) and non-Caucasians=299 patients (24%); of these non-Caucasians, 195 (65%) are black*), efficacy was consistent across race groups. However, for Study P128, (*Caucasians=1063 patients (80%) and non-Caucasians=271 patients (20%); of these non-Caucasians, 236 (87%) are black,* the test for treatment-by-race interaction was significant (p=0.006); the active treatment groups had more favorable responses than the placebo group for the Caucasian patients, the response of the non-Caucasian (Black, Hispanic, and "other" groups) was the opposite. It appears that the interpretation of this finding is confounded by the potential differences in response by site as the majority (76%) of the non-Caucasian patients were enrolled at 6 of the 15 investigator sites. This finding is unlikely to have been responsible for the absence of a statistically significant difference in the primary endpoint.

C. Evaluation of Pediatric Program

The applicant requested for waiver of pediatric studies in patients less than 12 years old. Currently, there is no plan to purse a non-prescription used for famotidine 20 mg for patients less than 12 years old.

D. Comments on Data Available or Needed in Other Populations

It has been used in the pediatric and geriatric population. The current prescription label states that no dosage adjustment is required based on age, however, because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. This submission did not reveal any issues particular to the geriatric population but the population was small to determine a definitive effect.

X. Conclusions and Recommendations

A. Conclusions

The three pivotal prevention studies (P114, P117 & P128) submitted by the applicant demonstrated that famotidine 20 mg is consistently and significantly more effective than placebo in preventing meal induced heartburn. This is proven by the all of the statistical endpoint outcomes.

Study P117 and P128 demonstrated that Famotidine 20 mg was superior to famotidine 10 mg with regard to the proportion of patients reporting no heartburn within 3 hours postmeal. Study P117 also demonstrated that Famotidine 20 mg was superior to famotidine 10 mg when peak heartburn severity was assessed during 3 hours postmeal; this is an outcome supported by Study P128 which showed a borderline statistical significance but has definitely shown a favorable numerical trend.

Patients in the famotidine 20mg group compared to the 10 mg group did not show consistent significant statistical difference with regard to the global assessment of efficacy measured at the end of the treatment period (all categories), proportion of patients reporting good/very good/global assessment and, no awakenings with heartburn.

Both treatment studies (P017 & P019) demonstrated that famotidine 20 mg was better than placebo when patients globally assessed their response to treatment; and when the proportion of heartburn episodes completely relieved within *1 hour* dosing was assessed, both famotidine 20 mg and 10 mg were significantly superior to placebo. In addition, patients who took famotidine 20 mg appear to

have a numerically greater probability of complete heartburn relief and more likely to report complete relief compared to those on famotidine 10 mg and placebo. Studies P017 and P019 were not statistically powered to differentiate the effect between famotidine 10 mg and 10 mg dose.

None of the studies showed significant statistical evidence that famotidine 20 mg or 10 mg was better over the other treatment groups in requiring back-up medication and re-medication. Famotidine 20 mg showed some numerically favorable results when assessing episodes requiring re-medication and no back-up medication.

It is known in clinical practice that famotidine is effective in treating gastrointestinal acid-related disorders (including GERD). It has been used as a prescription product for almost 17 years and as a nonprescription product for 8 years now.

In the proposed label, the bar graphs used by the applicant for prevention refers to the proportion of combined patients reporting "none" and "mild" heartburn severity during the 3 hours postmeal (Study C=P117 and Study D=P128). For treatment, the bar graphs were based on the median percentage of patients' episodes relieved within 1, 2, or 3 hours (Study A=P017 and Study B=P019).

B. Recommendations

From a clinical standpoint, efficacy evaluation from the studies submitted by the applicant supports the approval of famotidine 20 mg for the prevention of meal induced heartburn and treatment of episodic heartburn for non-prescription use. Final recommendation for approvability should be based on both safety and efficacy evaluation. A risk/benefit assessment for the indication of this drug will be performed by the Division of Over-the-Counter Drug Products.

From a clinical efficacy standpoint, this reviewer recommends over-the-counter use of famotidine 20 mg for prevention and treatment of *episodic* heartburn.

The proposed labeling for the dosing regimen and the directions for use in the relief and treatment of episodic heartburn are acceptable from an efficacy standpoint. The bar graphs proposed for prevention and treatment are acceptable, however, the sponsor should include "*10 minutes *Time taken before eating a meal that is expected to cause symptoms*" under *Study C* and *Study D* (similar to the 10 mg graph label). In these prevention studies, famotidine was taken 10 minutes prior to a provocative meal.

XI. Appendix

Individual More Detailed Study Reviews

A. Study P114
B. Study P117
C. Study P128
D. Study P017
E. Study P019

(Appendices are filed separately in DFS)

Appendix A

Reference P114

A Randomized, Single-Dose Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms when Administered 10 Minutes Prior to a Provocative Meal

Clinical Phase: III

Study Period: January 14, 1998 to March 17, 1998

Hypotheses and Objective:

Hypotheses

Primary:

- Patients dosed with famotidine 20 mg 10 minutes prior to a provocative meal will experience less severe heartburn than patients similarly dosed with famotidine 10 mg and similarly challenged, as measured by peak heartburn severity during the 3 hours following the start of the meal.

Secondary:

- Compared to famotidine 10 mg, famotidine 20 mg will produce a greater proportion of patients who do not awaken with heartburn and will have a more favorable global assessment of efficacy.
- Compared to placebo, famotidine 10 mg and famotidine 20 mg will produce a greater proportion of patients who do not awaken with heartburn and will have a more favorable global assessment of efficacy.
- Patients dosed with famotidine 20 mg or famotidine 10 mg 10 minutes prior to a provocative meal will experience less severe heartburn during the 3-hour postmeal period than patients dosed with placebo and similarly challenged as measured by peak heartburn severity, mean heartburn severity, and proportion of patients with no heartburn.
- Patients dosed with famotidine 20 mg 10 minutes prior to a provocative meal will experience less severe heartburn during the 3-hour postmeal period than patients dosed with famotidine 10 mg and similarly challenged, as measured by mean heartburn severity, and proportion of patients with no heartburn.

Objective

To assess the ability of famotidine 20 mg and famotidine 10 mg to prevent heartburn in patients treated 10 minutes prior to an evening provocative meal.

Study Design

Double-blind, randomized, double-dummy, single-dose, placebo-controlled, multicenter trial conducted with 3 parallel groups.

Famotidine 20-mg FCT, famotidine 10-mg FCT, and matching placebos were used as study medications. Ten investigational sites enrolled 1539 patients who participated in a screening meal session. A total of 793 patients completed the study.

During the screening session, patients received a 10-mg matching placebo FCT 10 minutes prior to ingesting a provocative meal (consisting of chili and cola). Heartburn symptoms were evaluated immediately prior to dosing and at 30-minute intervals for 3 hours beginning 30 minutes after the start of the meal. Those who developed heartburn symptoms of at least Grade 3 (severe) intensity during the screening meal session were eligible for randomization into the double-blind treatment session then returned to the facility between 7 to 15 days for participation.

Qualified patients at each investigative site were randomized to 1 of 3 groups according to a randomization schedule:

Treatment A - Famotidine 20-mg FCT/Famotidine 10-mg matching placebo FCT
Treatment B - Famotidine 10-mg FCT/Famotidine 20-mg matching placebo FCT
Treatment C - Famotidine 20-mg matching placebo FCT/Famotidine 10-mg matching placebo FCT

Prior to the dose of study medication, the patient assessed the presence of heartburn. Patients were dismissed if heartburn was present prior to dosing. Ten minutes after the dose of study medication, patients consumed a provocative meal consisting of chili and cola. The patients assessed the presence of heartburn symptoms at 30-minute intervals beginning 30 minutes after the start of the meal and continued for 3 hours. Patients rated the severity of their heartburn using a four-point scale. Before leaving the clinic, patients received a bedtime snack consisting of a chocolate brownie and fruit punch and a take-home diary to record any overnight heartburn symptoms. In the morning, patients recorded the times they awakened with heartburn or used rescue antacid, and answered the global evaluation of the study medication. Patients returned to the clinic within 3 days and reviewed and returned their diary and discussed any adverse experiences.

Patients with unbearably severe symptoms may have taken rescue medication, but they were asked not to take the rescue until at least 3 hours after the provocative meal. The rescue medication consisted of MYLANTA™ Double-Strength antacid tablets. Any patient taking rescue at any time following treatment was considered a "treatment failure" in the statistical analyses.

Concomitant Medication(s)

Prohibited

- OTC H2-receptor antagonists for the relief of heartburn or prescription medications for gastrointestinal disease, e.g., sucralfate, nizatidine, cimetidine, ranitidine, cisapride, famotidine, misoprostol, or metoclopramide from 7 days prior to screening until study completion.
- lansoprazole or omeprazole from 4 weeks prior to the screening meal until study completion.

- chronic use of nonsteroidal anti-inflammatory drugs, orally administered corticosteroids, anticholinergics, anticoagulants, tranquilizers, tricyclic antidepressants, or antineoplastics.
- if other conditions emerged that required drug therapy during this study, it will be recorded on the workbooks.
- OTC H2-receptor antagonists should be discontinued for 1 week prior to the screening meal. The patient may have replaced with antacid usage up to 12 hours prior to the start of the study session.

Permitted
- Antacid usage up to 12 hours prior to the start of the study session.
- Acetaminophen may have been taken for minor discomforts, and aspirin may have been taken at low doses (325 mg/day) for prophylactic anticoagulation.
- None of these medications were to be taken on the day of the study session.

Study Population

Inclusion Criteria
- Cooperative and reliable male or female patients age 18 or older.
- History of moderate to severe food-induced heartburn of at least 2 months duration with at least 3 episodes per week, and must have used antacids and/or OTC H2 –receptor antagonists for relief of symptoms.
- Signed written consent.
- Able to communicate well.

Exclusion Criteria
- History of a serious medical condition or evidence of impaired renal function.
- History of duodenal ulcer, gastric ulcer, atrophic gastritis, or diverticulitis within 2 years prior to study start; and history of upper GI tract surgery or vagotomy, esophageal strictures or Barrett's esophagus, endoscopically identified erosive esophagitis of moderate or greater severity, Zollinger-Ellison syndrome, irritable colon, inflammatory bowel disease, biliary tract disease, or known cholecystolithiasis.
- Known pregnancy or lactation. Women of childbearing potential must have been using adequate means of contraception.
- Recent use (within 1 week of the screening meal session) or continued treatment during the study of H_2-receptor antagonist or medication that modifies acid secretion. Use of omeprazole or lansoprazole within 4 weeks prior to study start. Chronic use of nonsteroidal anti-inflammatory drugs, orally administered corticosteroids, anticholinergics, anticoagulants, tranquilizers, tricyclic antidepressants, or antineoplastics were prohibited.
- History of drug or alcohol abuse, psychosis, or other condition making the patient unlikely to comply with the protocol.
- Administration of an investigational drug within 30 days prior to start of this study or within five half-lives of the investigational drug, whichever was longer.
- Participation in a heartburn study within 3 months prior to study start.

- Patients with a prior adverse reaction to antacids, H2 -receptor antagonists, any of the components of the study medication, or a prior adverse reaction to any ingredient(s) of the provocative meals or bedtime snack.
- Other conditions that would interfere with data interpretation or create undue risk.

Medical Officer Comment: The inclusion and exclusion criteria are appear adequate for this study.

Clinical Observations and Laboratory Measurements
There were no laboratory measurements in this study.
The schedule of clinical observations is provided in Table 1 and Table 2.

Table 1--Overall Study Flow Chart

Procedure	Preliminary Screening	Screening Session†	Treatment Session‡	Follow-Up§
Medical history	X			
Evaluate inclusion/exclusion	X			
Informed consent	X			
Screening placebo		X		
Study medication			X	
Provocative meal		X	X	
Complete diary card assessments		X	X	
Bedtime snack (eaten at home after departing clinic)			X	
Complete diary card assessments (at home)			X (next AM)	
Adverse experience monitoring		X	X	X
Concomitant medications	X	X	X	X
Review patient diary card		X	X	X

† Visit occurred within 15 days of preliminary screening.
‡ Visit occurred within 7 to 15 days of screening session.
§ Visit occurred within 72 hours of treatment session.
Adapted from electronic submission RefP114p.20

Study Flow Chart 2--Pre-Meal Procedures

	Time Before Clinic Visit			
Approximate Timing	-48:00	-24:00	-12:00	-5:00
Restrict alcohol intake to ≤2 drinks per day	X			
Avoid foods that typically produce heartburn until test meal		X		
Discontinue use of antacids			X	
Discontinue all alcohol			X	
Fast until provocative meal				X

Adapted from(Vol. 2-21)

Evaluation Criteria

Efficacy: heartburn severity evaluations (0=none, 1=mild, 2=moderate, 3=severe) at 30-minute intervals for the 3-hour period after both the screening and treatment meals, and a global evaluation of efficacy (0=poor, 1=fair, 2=good, 3=very good, 4=excellent) on the morning after treatment. Awakenings with heartburn and rescue medication use were also collected.

Safety: adverse experiences were reported during the screening and treatment meal sessions through 8 AM the following morning. Adverse experiences were graded as:

None -- No symptoms
Mild -- Awareness of sign or symptom but easily tolerated
Moderate -- Discomfort enough to cause interference with usual activity
Severe -- Incapacitating with inability to work or do usual activity

Adverse experiences were evaluated as to their severity, seriousness, relationship to test drug, action taken, and outcome.

Statistical Planning and Analysis

The treatment groups were compared with respect to:

(1) peak heartburn severity during the 3 hours following the start of the provocative meal (primary parameter). The primary treatment comparison was famotidine 20 mg versus 10 mg.

The treatment groups were also compared with respect to:

(2) the proportion of patients who reported no heartburn symptoms during the 3 hours following the start of the meal.
(3) global assessment of efficacy measured at the end of the treatment period were analyzed using logistic regression models for ordered categorical data.
(4) the proportion of patients who did not awaken with heartburn were analyzed using logistic regression models for binary data.
(5) mean heartburn severity during the 3 hours following the start of the meal was analyzed using an ANOVA model.

All models included factors for treatment group and investigator site. Because only one treatment comparison was performed for the primary hypothesis (famotidine 20 mg versus famotidine 10 mg for peak heartburn severity), no correction for multiple comparisons was made. Sample size: n=260 patients per treatment group had from 73 to 99% power to detect an 11- to 20-percentage-point difference between famotidine 20 mg and famotidine 10 mg for percentage of patients with none or mild peak heartburn during the 3 hours following the start of the provocative meal (α=two-tailed).

Ethics

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Results

Patient Characteristics

Baseline Patient Characteristics by Treatment Group
All-Patients-Treated (N=794)

	Famotidine 20 mg (n=261)	**Famotidine 10 mg** (n=271)	**Placebo** (n=262)	**Total** (n=794)
Age (Years)				
Mean	40.5	39.8	41.0	40.4
SD	12.2	12.1	12.2	12.2
Median	38.0	39.0	39.0	39.0
Range	19 to 81	19 to 72	18 to 77	18 to 81
N	261	271	262	794
Gender				
Male	87 (33.3%)	87 (32.1%)	84 (32.1%)	258 (32.5%)
Female	174 (66.7%)	184 (67.9%)	178 (67.9%)	536 (67.5%)
Racial Origin				
Caucasian	184 (70.5%)	187 (69.0%)	183 (69.8%)	554 (69.8%)
Black	58 (22.2%)	62 (22.9%)	60 (22.9%)	180 (22.7%)
Hispanic	17 (6.5%)	20 (7.4%)	18 (6.9%)	55 (6.9%)
Native American	1 (0.4%)	2 (0.7%)	1 (0.4%)	4 (0.5%)
Asian	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Height (Inches)				
Mean	66.5	66.4	66.3	66.4
SD	4.1	3.7	3.9	3.9
Median	66.0	66.0	66.0	66.0
Range	56 to 77	55 to 77	58 to 78	55 to 78
N	261	271	262	794
Body Weight (Lbs)				
Mean	182.9	180.6	182.1	181.9
SD	45.5	46.8	41.7	44.7
Median	180.0	178.0	180.0	180.0
Range	95 to 324	105 to 400	103 to 300	95 to 400
N	261	271	262	794

Adapted from electronic submission P114 p. 31

Medical Officer Comments: The majority of patients were Caucasians (70%), and the mean age was 40 years with age range from 18-81 years. There were twice as many females as there are males for each treatment arm. In terms of demographics, the treatment groups were well balanced.

Baseline Patient Characteristics by Treatment Group
All-Patients-Treated (N=794)

	Famotidine 20 mg (n=261)	Famotidine 10 mg (n=271)	Placebo (n=262)	Total (n=794)
Typical Heartburn Severity				
Very mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	14 (5.4%)	13 (4.8%)	8 (3.1 %)	35 (4.4%)
Moderately severe	124 (47.5%)	136 (50.2%)	126 (48.1%)	386 (48.6%)
Severe	109 (41.8%)	104 (38.4%)	110 (42.0%)	323 (40.7%)
Very severe	14 (5.4%)	18 (6.6%)	18 (6.9%)	50 (6.3%)
Heartburn Episodes Per Week				
Mean	5.1	5.3	5.1	5.2
SD	2.2	2.4	2.2	2.3
Median	5.0	4.0	5.0	5.0
Range	3 to 25	3 to 20	3 to 23	3 to 25
N	261	271	262	794
Number Severe if Untreated				
Mean	4.5	4.6	4.5	4.6
SD	2.3	2.3	2.2	2.3
Median	4.0	4.0	4.0	4.0
Range	1 to 25	1 to 15	0 to 23	0 to 25
N	260	271	262	793
Percent Severe if Untreated				
Mean	87.1	88.4	88.7	88.1
SD	18.6	19.1	18.1	18.6
Median	100.0	100.0	100.0	100.0
Range	20 to 100	25 to 100	0 to 100	0 to 100
N	260	271	262	793
Heartburn Med. Prior to Meal?				
No	190 (72.8%)	190 (70.1%)	195 (74.4%)	575 (72.4%)
Yes	71 (27.2%)	81 (29.9%)	67 (25.6%)	219 (27.6%)
Does Med. Completely Prevent Heartburn?				
No	43 (16.5%)	49 (18.1%)	50 (19.1%)	142 (17.9%)
Yes	24 (9.2%)	31 (11.4%)	15 (5.7%)	70 (8.8%)

Adapted from electronic submission (P114 p.33)

Medical Officer Comments: In terms of heartburn severity, majority of patients had moderately severe to severe heartburn with a mean of 5 episodes per week. With regard to typical heartburn severity, there were slightly more subjects with very severe heartburn in the Famotidine 10 mg (6.6%) and placebo group (6.9%) compared to the famotidine 20 mg group (5.4%).

The majority of patients (≥ 82% in each treatment group) were on some sort of therapy prior to the time of enrollment. The most common prior drug therapies in each of the treatment groups were antacids (calcium carbonate and dihydroxyaluminum sodium carbonate). The most common concomitant therapy in each treatment group was calcium carbonate.

Patient Accounting

Patient Accounting for All Randomized Patients

	Famotidine 20 mg n (%)	Famotidine 10 mg n (%)	Placebo n (%)	Total n (%)
Total randomized	261	271	262	794
Completed study	261 (100)	270 (99.6)	262 (100)	793 (99.9)
Discontinued study	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Patient uncooperative	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)

Adapted from (Vol. 2-39)

All 794 randomized patients took study medication and therefore all were included in the all-patients-treated population. Because only 5 patients (<1% of the all-patients-treated population) were considered major protocol violators, no per-protocol analyses were performed.

Distribution of "Treatment Failures" (n=298)
All-Patients-Treated (N=794)

	Famotidine 20 mg (n=261)	Famotidine 10 mg (n=271)	Placebo (n=262)	Total (n=794)
	n (%)	n (%)	n (%)	n (%)
Total "Treatment Failures"	84 (32.2)	97 (35.8)	117 (44.7)	298 (37.5)
Rescue at clinic	1 (0.4)	1 (0.4)	2 (0.8)	4 (0.5)
Antacid at home/before bed	28 (10.7)	39 (14.4)	45 (17.2)	112 (14.1)
Antacid overnight	27 (10.3)	27 (10.0)	25 (9.5)	79 (9.9)
Rescue at clinic and Antacid at home/before bed	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.3)
Rescue at clinic and Antacid overnight	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Antacid at home/before bed and Antacid overnight	27 (10.3)	28 (10.3)	41 (15.6)	96 (12.1)
Rescue at clinic, Antacid at home/before bed and Antacid overnight	1 (0.4)	1 (0.4)	2 (0.8)	4 (0.5)

Adapted from electronic submission P114 p.41

Medical Officer Comments: There were a total of 298 (37.5%) patients considered as "treatment failures". The Famotidine 20mg group has the least number of treatment failure (32.2%) followed by the famotidine 10mg group (35.8%). The placebo group has the most number of treatment failure (44.7%).

Efficacy Results

There was no evidence of a treatment-by-investigator interaction (p>0.050) for any of the efficacy parameters, indicating that the treatment effect was consistent across investigator sites. Also, for the primary efficacy parameter, there was no evidence of a treatment-by-factor interaction (p>0.050) for any of the demographic characteristics tested (age, gender, and race.

Primary Parameter:

The following tables and figure displays the results of the peak heartburn severity during the 3 hours following the start of the provocative meal.

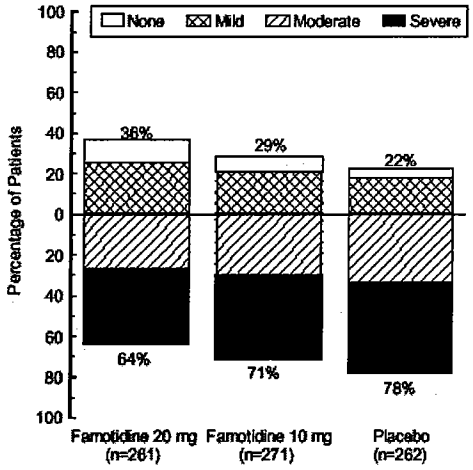
Peak Heartburn Severity During the 3 Hours Postmeal
All-Patients-Treated Approach (N=794)

	Famotidine 20 mg (n=261)	Famotidine 10 mg (n=271)	Placebo (n=262)
	n (cum %)	n (cum %)	n (cum %)
None	28 (10.7)	21 (7.7)	11 (4.2)
Mild	67 (36.4)	57 (28.8)	47 (22.1)
Moderate	71 (63.6)	81 (58.7)	89 (56.1)
Severe	95 (100.0)	112 (100.0)	115 (100.0)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg vs. Famotidine 10 mg [P]	1.34 (0.98, 1.84)	3.42	0.064
Famotidine 20 mg vs. Placebo	1.73 (1.26, 2.39)	11.38	<0.001
Famotidine 10 mg vs. Placebo	1.29 (0.94, 1.77)	2.47	0.116
[P] = Primary treatment comparison.			

Adapted from electronic submission P114 p.34

Peak Heartburn Severity During the 3 Hours Postmeal



Adapted from electronic submission P114 p.44

Medical Officer Comments: The peak heartburn severity during the 3 hrs. postmeal show that the difference between famotidine 20 mg and placebo was statistically significant ($p<0.001$). However, the difference between the famotidine 20 mg and 10 mg was marginally significant ($p=0.064$); and the famotidine 10 mg versus placebo difference was not statistically significant ($p=0.116$). The odds-ratios indicate that famotidine 20-mg patients were 1.34 and 1.73 times more likely to report less severe peak symptoms than famotidine 10-mg and placebo patients, respectively.

Secondary Parameters:

1) The tables below show the proportion of patients reporting no heartburn during the 3 hours following the start of the meal

Proportion of Patients Reporting No Heartburn Symptoms
During the 3 Hours Postmeal
All-Patients-Treated Approach (N=794)

	Famotidine 20 mg (n=261)		Famotidine 10 mg (n=271)		Placebo (n=262)	
	n	(%)	n	(%)	n	(%)
No Heartburn	28	(10.7)	21	(7.7)	11	(4.2)
Any Heartburn	233	(89.3)	250	(92.3)	251	(95.8)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg vs. Famotidine 10 mg	1.44 (0.78, 2.65)	1.37	0.241
Famotidine 20 mg vs. Placebo	2.91 (1.40, 6.07)	8.14	0.004
Famotidine 10 mg vs. Placebo	2.02 (0.94, 4.34)	3.28	0.070

Adapted from electronic submission P114 p.45

Medical Officer Comments: Although not statistically significant, there were more patients with no heartburn in the famotidine 20-mg group (10.7%) than the famotidine 10-mg group (7.7%). Both famotidine groups showed a greater proportion of patients who reported no heartburn compared to the placebo group. There was a statistically significant difference between the famotidine 20-mg versus placebo. The famotidine 10-mg versus placebo difference was marginally significant ($p=0.070$).

2) Below is a table showing the mean heartburn severity during the 3 hours following the start of the meal

Mean Heartburn Severity During the 3 Hours Postmeal

Treatment Group	n	Mean†	Standard Error
Famotidine 20 mg	261	1.20	0.051
Famotidine 10 mg	271	1.32	0.050
Placebo	262	1.46	0.051
† 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe			

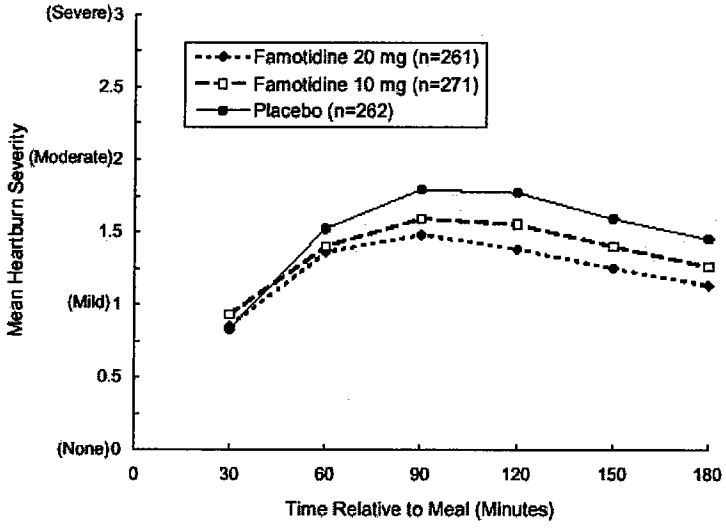
Treatment Comparison	Mean Difference (95% CI)	F-Statistic	p-Value
Famotidine 20 mg vs. Famotidine 10 mg	-0.11 (-0.25, 0.02)	2.62	0.106
Famotidine 20 mg vs. Placebo	-0.26 (-0.39, -0.12)	13.00	<0.001
Famotidine 10 mg vs. Placebo	-0.14 (-0.28, -0.00)	4.08	0.044

Adapted from electronic submission P114 p46)

Medical Officer Comments:
Both famotidine groups had less severe mean symptoms compared to the placebo group. The difference between the 20mg and 10mg group was not statistically significant (p=0.106).

The figure below shows the two famotidine groups begin to show a separation from placebo at 60 minutes postmeal, and the famotidine 20-mg group begins to separate from famotidine 10 mg at about 90 minutes postmeal.

Mean Heartburn Severity From 30 Minutes to 3 Hours Postmeal
All-Patients-Treated Approach (N=794)



Note: "Severe" assigned for patients after use of rescue medication.

Adapted from electronic submission P114 p47

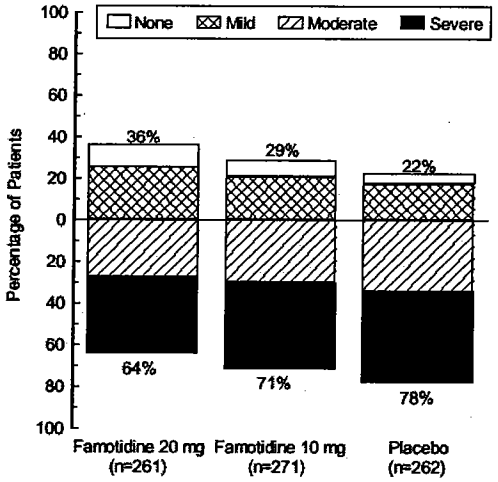
3) The tables and figure below shows the global assessment of efficacy measured at the end of the treatment period.

Global Assessment of Efficacy--All-Patients-Treated Approach (N=793)

	Famotidine 20 mg (n=261)		Famotidine 10 mg (n=270)		Placebo (n=262)	
	n	(cum %)	n	(cum %)	n	(cum %)
Excellent	37	(14.2)	28	(10.4)	16	(6.1)
Very Good	65	(39.1)	59	(32.2)	47	(24.0)
Good	44	(55.9)	40	(47.0)	40	(39.3)
Fair	21	(64.0)	34	(59.6)	33	(51.9)
Poor	94	(100.0)	109	(100.0)	126	(100.0)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Proportion of Patients Reporting Good, Very Good, or Excellent			
Famotidine 20 mg vs. Famotidine 10 mg	1.44 (1.02, 2.04)	4.32	0.038
Famotidine 20 mg vs. Placebo	2.02 (1.42, 2.87)	15.15	<0.001
Famotidine 10 mg vs. Placebo	1.40 (0.99, 1.98)	3.52	0.061
All Categories			
Famotidine 20 mg vs. Famotidine 10 mg	1.33 (0.97, 1.80)	3.22	0.073
Famotidine 20 mg vs. Placebo	1.94 (1.41, 2.66)	16.90	<0.001
Famotidine 10 mg vs. Placebo	1.46 (1.07, 2.00)	5.65	0.017

Adapted from electronic submission P114 p49



Adapted from sponsor's electronic submission P114 p50

Medical Officer Comments: The famotidine 20-mg group reported more favorable global assessments compared to both famotidine 10-mg and placebo groups. For the analysis of the proportion of patients reporting good, very good, or excellent global assessments, both comparisons of 20 mg versus 10 mg and placebo were statistically significant. For the

analysis across all categories of global assessment, the famotidine 20-mg versus placebo comparison was again statistically significant (p<0.001), but the famotidine 20-mg versus famotidine 10-mg comparison was only marginally significant (p=0.073).

4) The following tables show the proportion of patients reporting no awakenings with heartburn.

Proportion of Patients Reporting No Awakenings With Heartburn
All-Patients-Treated Approach (N=792)

	Famotidine 20 mg (n=261)		Famotidine 10 mg (n=269)		Placebo (n=262)	
	n	(%)	n	(%)	n	(%)
No Awakenings	156	(59.8)	153	(56.9)	113	(43.1)
Any Awakenings	105	(40.2)	116	(43.1)	149	(56.9)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg vs. Famotidine 10 mg	1.13 (0.79, 1.59)	0.44	0.505
Famotidine 20 mg vs. Placebo	1.99 (1.40, 2.82)	14.78	<0.001
Famotidine 10 mg vs. Placebo	1.77 (1.25, 2.50)	10.39	0.001

Adapted from electronic submission Ref P114 p51

Medical Officer Comments: These results demonstrate that the famotidine groups were similar with respect to this parameter (p=0.505) and significantly greater proportions of patients in these groups reported no awakenings with heartburn compared to the placebo group.

Summary of Efficacy Comparisons

Summary of Efficacy Comparisons
All-Patients-Treated Approach

Efficacy Parameter	FAM 20 mg vs. FAM 10 mg	FAM 20 mg vs. Placebo	FAM 10 mg vs. Placebo
PRIMARY			
Peak heartburn during 3 hours postmeal	[P] 0.064 +	<0.001 **	0.116
SECONDARY			
% Reporting no heartburn during 3 hours postmeal	0.241	0.004 **	0.070 +
Mean heartburn severity during 3 hours postmeal	0.106	<0.001 **	0.044 *
Global assessment of efficacy measured at end of treatment period (all categories)	0.073 +	<0.001 **	0.017 *
% Good/Very Good/Excellent global assessment	0.038 *	<0.001 **	0.061 +
% Reporting no awakenings with heartburn	0.505	<0.001 **	0.001 **

[P] = Primary treatment comparison.
FAM = Famotidine.
+ $0.05 < p \leq 0.10$; * $p \leq 0.05$; ** $p \leq 0.01$

Adapted from electronic submission Ref P114 p52

The results of the interim analysis (n=596) were generally consistent with the final results.

Subgroup Analysis

There was no evidence of a treatment-by-investigator interaction (p>0.050) for any of the efficacy parameters. See tables below.

Peak Heartburn Severity During the 3 Hours Postmeal
By Age Group
All-Patients-Treated Approach (N=794)

			None	Mild	Moderate	Severe
Treatment Group	Age Group	n	n (cum %)	n (cum %)	n (cum %)	n (cum %)
Famotidine 20 mg	65 or under	251	26 (10.4)	66 (36.7)	67 (63.3)	92 (100.0)
	Over 65	10	2 (20.0)	1 (30.0)	4 (70.0)	3 (100.0)
Famotidine 10 mg	65 or under	261	20 (7.7)	55 (28.7)	78 (58.6)	108 (100.0)
	Over 65	10	1 (10.0)	2 (30.0)	3 (60.0)	4 (100.0)
Placebo	65 or under	255	11 (4.3)	46 (22.4)	87 (56.5)	111 (100.0)
	Over 65	7	0 (0.0)	1 (14.3)	2 (42.9)	4 (100.0)

Adapted from electronic submission RefP114p.390

Medical Officer Comments:Less than 5% of the population in each group were ≥ 65 years old, the number is too small to do meaningful analysis.

Peak Heartburn Severity During the 3 Hours Postmeal
By Race
All-Patients-Treated Approach (N=794)

			None	Mild	Moderate	Severe
Treatment Group	Race	n	n (cum %)	n (cum %)	n (cum %)	n (cum %)
Famotidine 20 mg	Caucasian	184	26 (14.1)	55 (44.0)	48 (70.1)	55 (100.0)
	Non-Caucasian	77	2 (2.6)	12 (18.2)	23 (48.1)	40 (100.0)
Famotidine 10 mg	Caucasian	187	19 (10.2)	45 (34.2)	62 (67.4)	61 (100.0)
	Non-Caucasian	84	2 (2.4)	12 (16.7)	19 (39.3)	51 (100.0)
Placebo	Caucasian	183	8 (4.4)	37 (24.6)	70 (62.8)	68 (100.0)
	Non-Caucasian	79	3 (3.8)	10 (16.5)	19 (40.5)	47 (100.0)

Adapted from electronic submission RefP114 Appendix 4.1.11.

For the primary efficacy parameter, there was no evidence of a treatment-by-factor interaction (p>0.050) for race (Caucasian vs. non-Caucasians).

Safety

For safety evaluation, please see OTC medical Officer's Safety Review

Summary of Statistical Endpoint Outcomes

Summary of Statistical Endpoint Outcomes

Secondary Efficacy Parameters	FAM 20 mg vs. FAM 10 mg	FAM 20 mg vs. Placebo	FAM 10 mg vs. Placebo
% Reporting no heartburn during 3 hours postmeal	—	**	+
Mean heartburn severity during 3 hours postmeal	—	**	*
Global assessment of efficacy measured at end of treatment period (all categories)	+	**	*
% Good/Very Good/Excellent global assessment	*	**	+
% Reporting no awakenings with heartburn	—	**	**

FAM = Famotidine.

+ $0.05 < p \leq 0.10$; * $p \leq 0.05$; ** $p \leq 0.01$; — Not significant

Sponsor's table from Ref. P114p58

Discussion

Medical Officer Comments:
Reference P114 is a single-dose study that compared famotidine 20 mg, famotidine 10 mg and placebo in preventing heartburn symptoms 10 minutes prior to a provocative meal. The patients who participated in the study were mostly middle-aged Caucasians with self-identified severe heartburn who qualified by reporting severe symptoms in response to a standard provocative meal challenge.

In this study, for reporting peak heartburn severity, famotidine 20 mg was more effective than placebo ($p<0.001$), the difference between the famotidine 20 mg and 10 mg was marginally significant ($p=0.064$), and the famotidine 10 mg dose was no better than placebo.

The study further shows that famotidine 20 mg was more effective than placebo in reporting no heartburn and mean heartburn severity during 3 hours postmeal, global assessment of efficacy, and no awakenings with heartburn. The 20mg dose was more effective than the 10mg dose with global assessment of efficacy in preventing heartburn. Both famotidine groups demonstrated a significantly smaller proportion of patients awakened with heartburn compared to placebo; however, this did not discern a difference between the famotidine doses.

There was no evidence of a treatment-by-factor interaction ($p>0.050$) for any of the demographic characteristics tested (age, gender, and race) in this study.

For details of safety assessment, please see the Agency's Division of Over-the-Counter Drugs Medical Officer's Review.

Appendix B

Reference P117
A Randomized, Single-Dose Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered 10 Minutes Prior to a Provocative Meal

Clinical Phase: III

Study period: July, 1998 to September, 1998

Hypotheses and Objectives:

Hypotheses

Primary:

- Patients dosed with famotidine 20 mg 10 minutes prior to a provocative meal will experience less severe heartburn than patients similarly dosed with famotidine 10 mg and similarly challenged, as measured by peak heartburn severity during the 3 hours following the start of the meal.

Secondary:

- Compared to patients dosed with famotidine 10 mg 10 minutes prior to a provocative meal, patients similarly dosed with famotidine 20 mg and similarly challenged will experience less severe heartburn (as measured by mean heartburn severity during the 3 hours following the start of the meal) and will report more favorable global assessments of efficacy.

Objective

To assess the ability of famotidine 20 mg and famotidine 10 mg to prevent heartburn in patients treated 10 minutes prior to an evening provocative meal.

Study Population

Inclusion Criteria

- Male or female patients who were at least 18 years of age or older; cooperative, reliable, and of adequate intelligence to grade and record symptoms as requested.
- History of food-induced heartburn of at least 2 months' duration with at least 3 episodes per week, and that was frequently severe (30% of their episodes) and able to identify specific foods and beverages that produced symptoms; and used antacids and/or OTC H2 -receptor antagonists.
- Must have signed the informed consent.

Exclusion Criteria

- History of a serious medical condition or evidence of impaired renal function.
- History of duodenal ulcer, gastric ulcer, atrophic gastritis, or diverticulitis within 2 years prior to study start; and a history of upper GASTROINTESTINAL tract surgery or

vagotomy, esophageal strictures or Barrett's esophagus, endoscopically identified erosive esophagitis of moderate or greater severity, Zollinger-Ellison syndrome, irritable colon, inflammatory bowel disease, biliary tract disease, or known cholecystolithiasis.

- Pregnant or lactating. Women of childbearing potential used adequate means of contraception.
- Recently used (within 1 week of the treatment meal) or continued use of medication which modified acid secretion. Used omeprazole or lansoprazole within the 4 weeks prior to the treatment meal.
- Chronic use of nonsteroidal anti-inflammatory drugs, orally administered corticosteroids, anticholinergics, anticoagulants, tranquilizers, tricyclic antidepressants, or antineoplastics.
- Recently used (within 1 week of the treatment meal) OTC H2 –receptor antagonists. If the patient used these for the relief of heartburn, the patient discontinued the usage for 1 week prior to the treatment meal session and replaced with antacid usage up to (but not including) the day of the study session.
- Recent history of habituating drug or alcohol abuse, psychosis, or other condition making the patient unlikely to comply with the protocol.
- Use of an investigational drug within 30 days prior to start of this study or within five half-lives of the investigational drug, whichever was longer.
- Previously participated in a heartburn study (within 3 months prior to study start).
- Prior adverse reaction to antacids, H2 antagonists, any of the components of the study medication, or a prior adverse reaction to any ingredient(s) of the provocative meals or bedtime snack.
- Other conditions that would interfere with data interpretation or create undue risk.

Medical Officer Comment: The inclusion and exclusion appear adequate for this study.

Study Design

This was a multicenter, double-blind, double-dummy, randomized, parallel, single-dose study.

There were 1799 patients enrolled in the baseline run-in period to evaluate their heartburn over a 1-week period. To participate in the run-in period, patients had at least a 2-month history of food-induced heartburn occurring three or more times per week. Patients experienced meal-induced heartburn that was frequently severe (30% of their episodes). Patients were able to identify specific foods and beverages that produced symptoms and used antacids and/or OTC H2 -receptor antagonists for effective relief of their symptoms. A total of 1229 patients were randomized to receive study drug. A total of 1225 patients completed the double-blind portion of the study. The treatment ratio was 2:2:1 (20 mg: 10 mg: PBO) within each site.

During the baseline period the patients were given a 1-week, take-home diary card to confirm their eligibility for randomization into the double-blind treatment session. No study medication was provided during the baseline run-in period. The patients recorded the time and date of each episode of heartburn, severity of the episode, and if antacid or H2 antagonist was taken. Patients were also asked the question, "Was the episode of heartburn you experienced brought on by consuming food or beverage?" Patients satisfied all of the following criteria to be eligible to enter the treatment meal session:

• Had meal/beverage-induced heartburn, at least 3 times in the 1-week period, and at least 3 of the episodes were treated with antacid or H2 -receptor antagonists.
• At least 1 of their episodes during that 1-week period was considered severe (heartburn severity was determined by self evaluation).
• Satisfactorily completed the diary card.

Eligible patients returned to the study facility no later than 15 days after returning their baseline diary cards for participation in the treatment meal session. During the treatment session, patients were required to remain at the study facility for a 4-hour period.

The treatments used were famotidine 20-mg FCT, famotidine 10-mg FCT, and matching placebos. Patients fasted (except for water) for 5 hours before reporting to the study facility at approximately 6 PM. Prior to the dose of study medication, the patient was assessed for the presence of heartburn. Patients were dismissed if heartburn was present prior to dosing. Ten minutes after the dose of study medication, patients consumed a provocative meal consisting of chili, cola, and a chocolate bar. The patients evaluated their heartburn symptoms at 30-minute intervals beginning 30 minutes after the start of the meal and continuing for 3 hours. Patients rated the severity of their heartburn using a four-point scale. At the conclusion of the meal, all patients (including those who used rescue medication during the 3-hour assessment period), received their take-home diary card, instructions, and bedtime snack consisting of a brownie and fruit punch, and were released to go home at 10 PM. Patients ate all of the bedtime snack before retiring. The patients were encouraged to retire no later than 11 PM.

All patients were to record any overnight heartburn symptoms. In the morning, patients recorded the times they awoke during the night with heartburn or used rescue antacid, and answered the global evaluation question about the study medication. Patients returned to the clinic within 3 days to review and return their diary card and to discuss any adverse experiences.

Patients with unbearably severe symptoms could take rescue medication, at least 3 hours after the provocative meal. The rescue medication consisted of MYLANTA™ Double Strength antacid tablets. Any patient taking rescue at any time following treatment was considered a "treatment failure" in the statistical analyses.

If patients used OTC H2-receptor antagonists (PEPCID AC™ ACID CONTROLLER™, TAGAMET™ HB™, ZANTAC™ 75, AXID™ AR, MYLANTA™ AR) for the relief of heartburn, they discontinued usage for 1 week prior to the treatment meal. The patient could replace with antacid usage up to 12 hours prior to the start of the study session. Acetaminophen could be taken for minor discomforts, and aspirin could be taken at low doses (325 mg/day) for prophylactic anticoagulation and documented on the case report form. None of these medications could be taken within the 12 hours prior to the start of the treatment meal session.

Overall Study Flow Chart

Procedure	Visit 1	Visit 2†	Visit 3‡ Treatment Session	Visit 4§ Follow-Up
Medical history (including heartburn history)	X			
Evaluate inclusion/exclusion	X			
Informed consent	X			
Dispense diary card for run-in week	X			
Study medication (double blind)			X	
Provocative meal			X	
Complete diary card assessments (in-clinic)			X	
Bedtime snack (eaten at home after departing clinic)			X	
Complete diary card assessments (at home)	X		X (through next AM)	X
Adverse experience monitoring		X	X	X
Prior/concomitant medications	X	X	X	X
Review patient diary card		X	X	X

† Visit occurred within 7 to 15 days of Visit 1.
‡ Visit occurred within 15 days of returning baseline diary card (Visit 2).
§ Visit occurred within 72 hours of treatment session (Visit 3).

Adapted from electronic submission RefP117p.21

Evaluation Criteria

Patients were provided with an in-clinic diary card to record their symptoms.

Efficacy:

- Heartburn severity evaluations at 30-minute intervals (1=mild, 2=moderate, 3=severe) for the 3-hour period (at 30-minute intervals) following the treatment meal.
- Heartburn symptoms experienced during the overnight evaluation period; and global evaluation of efficacy at end of the overnight evaluation period (0=poor, 1=fair, 2=good, 3=very good, 4=excellent).
- Beginning 3 hours after the start of the provocative meal, patients could take rescue medication (MYLANTA™ Double Strength antacid; 2 tablets) for treatment of symptoms.
- Patients were asked to record the number of times they awoke from sleep with heartburn symptoms and and the time of rescue medication, if taken.

Safety:

Adverse experiences were monitored throughout this study and evaluated as to:

- Maximum intensity
  - Mild (awareness of signs or symptom, but easily tolerated)
  - Moderate (discomfort enough to cause interference with usual activity)
  - Severe (incapacitating with inability to work or do usual activity)
- Seriousness
- Relationship to test drug (definitely, probably, possibly, probably not, definitely not related)

Statistical Planning and Analysis

The treatment groups were compared with respect to:

(1) Peak heartburn severity during the 3 hours following the start of the provocative meal (primary parameter).
(2) Global assessment of efficacy measured at the end of the treatment period were analyzed using logistic regression models for ordered categorical data
(3) The proportion of patients who reported no heartburn symptoms during the 3 hours following the start of the meal.
(4) The proportion of patients who did not awaken with heartburn.
(5) The proportion of patients who used rescue medication during the study were analyzed using logistic regression models for binary data.
(6) Mean heartburn severity during the 3 hours following the start of the meal was analyzed using an ANOVA model.

All models included factors for treatment group and investigator site. Because only one treatment comparison was performed for the primary hypothesis (famotidine 20 mg versus famotidine 10 mg for peak heartburn severity), no correction for multiple comparisons was made.

Sample size: n=500 patients per active treatment group and 250 patients in the placebo group had from 60 to 89% power to detect a 7- to 10-percentage-point difference between famotidine 20 mg and famotidine 10 mg, and from 73 to 95% power to detect a 10- to 14-percentage-point difference between active treatment group and placebo, for percentage of patients with none or mild peak heartburn during the 3 hours following the start of the provocative meal (a=0.050, two-tailed).

Ethics

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Results

Patient Characteristics

Baseline Patient Characteristics by Treatment Group

	Famotidine 20 mg (n=489)	Famotidine 10 mg (n=491)	Placebo (N=249)	Total (n=1229)
Age (years)				
Mean	42.3	41.6	42.3	42.0
SD	13.3	12.9	12.5	13.0
Median	41.0	40.0	41.0	41.0
Range	18 to 80	19 to 85	18 to 78	18 to 85
N	489	491	249	1229
Gender				
Male	190 (38.9%)	199 (40.5%)	105 (42.2%)	494 (40.2%)
Female	299 (61.1%)	292 (59.5%)	144 (57.8%)	735 (59.8%)
Racial Origin				
Caucasian	373 (76.3%)	366 (74.5%)	191 (76.7%)	930 (75.7%)
Black	76 (15.5%)	81 (16.5%)	38 (15.3%)	195 (15.9%)
Hispanic	39 (8.0%)	43 (8.8%)	17 (6.8%)	99 (8.1%)
Asian	1 (0.2%)	0 (0.0%)	3 (1.2%)	4 (0.3%)
American Indian	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Height (inches)				
Mean	66.9	66.8	67.2	66.9
SD	4.0	4.1	3.7	4.0
Median	67.0	67.0	67.0	67.0
Range	53 to 79	57 to 80	60 to 76	53 to 80
N	489	490	249	1228
Body Weight (lbs)				
Mean	180.8	183.0	180.9	181.7
SD	41.3	41.1	42.1	41.4
Median	180.0	180.0	178.0	180.0
Range	95 to 350	105 to 360	100 to 350	95 to 360
N	489	490	249	1228
Duration of Heartburn				
<2 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2 to 6 months	7 (1.4%)	10 (2.0%)	6 (2.4%)	23 (1.9%)
6 to 12 months	19 (3.9%)	21 (4.3%)	8 (3.2%)	48 (3.9%)
>12 months	463 (94.7%)	460 (93.7%)	235 (94.4%)	1158(94.2%)
Typical Heartburn Severity				
Very mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Moderate	48 (9.8%)	48 (9.8%)	21 (8.4%)	117 (9.5%)
Moderately severe	258 (52.8%)	269 (54.8%)	133 (53.4%)	660 (53.7%)
Severe	170 (34.8%)	153 (31.2%)	88 (35.3%)	411 (33.4%)
Very severe	11 (2.2%)	21 (4.3%)	7 (2.8%)	39 (3.2%)

Adapted from electronic submission RefP117p.37

Medical Officer Comments: The majority of patients were Caucasians (75%), and the mean age was 42 years with an age range of 18-85 years. There were more females than males (60% vs. 40%) for each treatment arm. Ninety-four percent of the patients in each treatment arm had heartburn for >12 months and majority had moderately severe to severe heartburn severity. There were twice as many patients in each of the famotidine group compared to the placebo group. In terms of baseline demographics, the treatment groups were well-balanced.

Patient Accounting

A total of 1229 patients were randomized to one of the three treatment groups, 1225 completed the study. See tables below.

Patient Accounting for All Randomized Patients (N=1229)

	Famotidine 20 mg		Famotidine 10 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Total randomized	489		491		249		1229	
Completed study	488	(99.8)	489	(99.6)	248	(99.6)	1225	(99.7)
Discontinued study	1	(0.2)	2	(0.4)	1	(0.4)	4	(0.3)
Clinical adverse experience	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
Lost to follow-up	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Protocol deviation	1	(0.2)	1	(0.2)	0	(0.0)	2	(0.2)

Adapted from electronic submission RefP117p.46

Distribution of "Treatment Failures" (n=328)
All-Patients-Treated (N=1227)

	Famotidine 20 mg (n=488)		Famotidine 10 mg (n=490)		Placebo (n=249)		Total (n=1227)	
	n	(%)	n	(%)	n	(%)	n	(%)
Total "Treatment Failures"	111	(22.7)	124	(25.3)	93	(37.3)	328	(26.7)
Rescue at clinic	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Antacid at home/before bed	37	(7.6)	44	(9.0)	50	(20.1)	131	(10.7)
Antacid overnight	51	(10.5)	45	(9.2)	24	(9.6)	120	(9.8)
Antacid at home/before bed and Antacid overnight	23	(4.7)	34	(6.9)	19	(7.6)	76	(6.2)

Adapted from electronic submission RefP117p.49

Medical Officer Comments: All 1229 randomized patients took study medication and therefore all were included in the all-patients-treated analyses. However, there were 53 patients who were major protocol violators, these were excluded in the per-protocol approach. Patients who had treatment failures were assigned the worst scores for heartburn evaluation.

Efficacy

The sponsor reported that there was no evidence of a treatment-by-investigator interaction ($p>0.050$) for any of the efficacy parameters, indicating that the treatment effect was consistent across investigator sites, and for the primary efficacy parameter (peak heartburn), there was no evidence of a treatment-by-factor interaction ($p>0.050$) for either age, race or gender.

Primary Parameter:

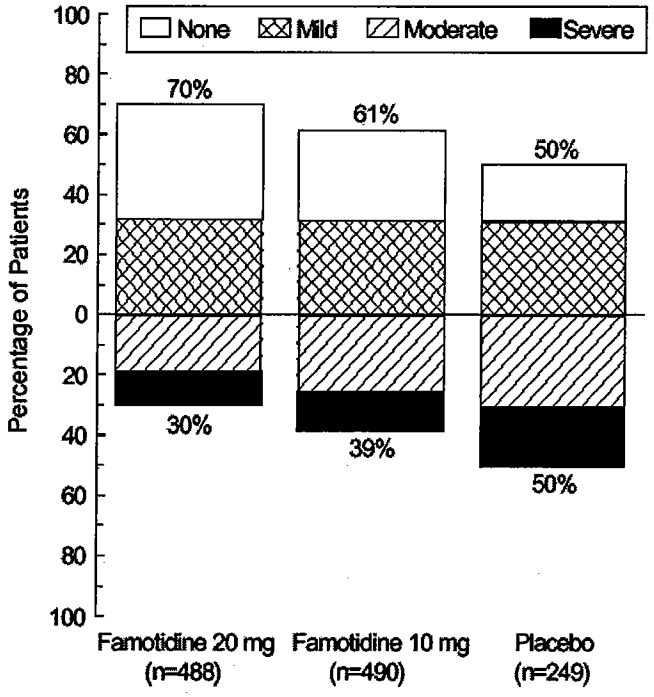
The tables below display the results of the peak heartburn severity during the 3 hours following the start of the provocative meal.

Peak Heartburn Severity During the 3 Hours Postmeal
All-Patients-Treated Approach (N=1227)

	Famotidine 20 mg (n=488)		Famotidine 10 mg (n=490)		Placebo (n=249)	
	n	(cum %)	n	(cum %)	n	(cum %)
None	185	(37.9)	147	(30.0)	47	(18.9)
Mild	156	(69.9)	153	(61.2)	77	(49.8)
Moderate	93	(88.9)	126	(86.9)	77	(80.7)
Severe	54	(100.0)	64	(100.0)	48	(100.0)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus famotidine 10 mg [P]	1.44 (1.14, 1.81)	9.57	0.002
Famotidine 20 mg versus placebo	2.47 (1.86, 3.27)	39.55	<0.001
Famotidine 10 mg versus placebo	1.71 (1.30, 2.26)	14.45	<0.001

[P] = Primary treatment comparison.



Adapted from electronic submission RefP117p.53-54

Medical Officer Comments: The results, as shown above demonstrates that both famotidine groups had less severe peak heartburn symptoms compared to the placebo group and the famotidine 20-mg group had significantly less severe peak heartburn symptoms than the famotidine 10-mg group (p=0.002). The odds-ratios indicate that famotidine 20-mg patients were 1.44 and 2.47 times more likely to report less severe peak symptoms than famotidine 10-mg and placebo patients, respectively.

Secondary Parameters:

1) The tables below show the proportion of patients reporting no heartburn during the 3 hours following the start of the meal.

Proportion of Patients Reporting No Heartburn Symptoms During the 3 Hours Postmeal
All-Patients-Treated Approach (N=1227)

	Famotidine 20 mg (n=488)	Famotidine 10 mg (n=490)	Placebo (n=249)
	n (%)	n (%)	n (%)
No Heartburn	185 (37.9)	147 (30.0)	47 (18.9)
Any Heartburn	303 (62.1)	343 (70.0)	202 (81.1)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus famotidine 10 mg	1.47 (1.12, 1.93)	7.50	0.006
Famotidine 20 mg versus placebo	2.74 (1.89, 3.99)	27.94	<0.001
Famotidine 10 mg versus placebo	1.87 (1.28, 2.74)	10.54	0.001

Adapted from electronic submission RefP117p.55

Medical Officer Comments: The results show that there was a greater percentage of patients with no heartburn symptoms in the famotidine 20-mg group compared to both the famotidine 10-mg (p=0.006) and the placebo (p<0.001) groups. The famotidine 10-mg group had a greater percentage of patients with no heartburn than the placebo group (p=0.001).

2) Mean Heartburn Severity During the 3 Hours Following the Start of the Meal

Mean Heartburn Severity During the 3 Hours Postmeal
All-Patients-Treated Approach (N=1227)

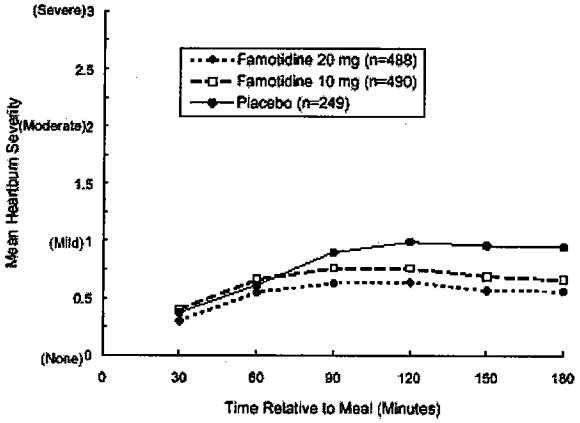
Treatment Group	n	Mean†	Standard Error
Famotidine 20 mg	488	0.53	0.030
Famotidine 10 mg	490	0.65	0.030
Placebo	249	0.78	0.042

† 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe

Treatment Comparison	Mean Difference (95% CI)	F-Statistic	p-Value
Famotidine 20 mg versus famotidine 10 mg	-0.11 (-0.20, -0.03)	7.46	0.006
Famotidine 20 mg versus placebo	-0.25 (-0.35, -0.15)	24.43	<0.001
Famotidine 10 mg versus placebo	-0.14 (-0.24, -0.04)	7.30	0.007

Adapted from electronic submission RefP117p.56

Mean Heartburn Severity From 30 Minutes to 3 Hours Postmeal
All-Patients-Treated Approach (N=1227)



Adapted from electronic submission RefP117p.57

Medical Officer Comments: The famotidine 20 mg group experienced significantly less severe mean heartburn symptoms as compared to the famotidine 10 mg (p=0.006) and placebo group (p<0.001). The famotidine 10 mg group had significantly less severe mean symptoms as compared to the placebo group (p=0.007).

3) Below are tables showing the global assessment of efficacy measured the next morning at the end of the treatment period.

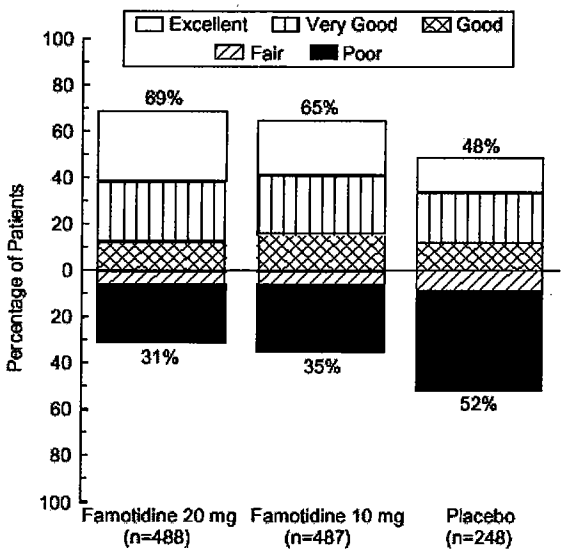
Global Assessment of Efficacy

All-Patients-Treated Approach (N=1223)

	Famotidine 20 mg (n=488)		Famotidine 10 mg (n=487)		Placebo (n=248)	
	n	(cum %)	n	(cum %)	n	(cum %)
Excellent	147	(30.1)	115	(23.6)	36	(14.5)
Very Good	126	(55.9)	125	(49.3)	54	(36.3)
Good	62	(68.6)	76	(64.9)	30	(48.4)
Fair	28	(74.4)	31	(71.3)	22	(57.3)
Poor	125	(100.0)	140	(100.0)	106	(100.0)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Proportion of Patients Reporting Good, Very Good, or Excellent			
Famotidine 20 mg versus famotidine 10 mg	1.20 (0.91, 1.58)	1.70	0.192
Famotidine 20 mg versus placebo	2.45 (1.78, 3.38)	29.74	<0.001
Famotidine 10 mg versus placebo	2.04 (1.49, 2.81)	19.31	<0.001
All Categories			
Famotidine 20 mg versus famotidine 10 mg	1.30 (1.04, 1.63)	5.13	0.024
Famotidine 20 mg versus placebo	2.40 (1.81, 3.18)	37.34	<0.001
Famotidine 10 mg versus placebo	1.85 (1.40, 2.44)	18.55	<0.001

Adapted from electronic submission RefP117p.59



Adapted from electronic submission RefP117p. 60

Medical Officer Comments: For the analysis across all categories of global assessment, the famotidine 20-mg group had significantly more favorable global assessment compared to both the famotidine 10-mg (p=0.024) and placebo (p<0.001) groups; for the analysis of the proportion of patients reporting good, very good, or excellent global assessments, the comparison versus placebo was statistically significant (p<0.001), but not the comparison versus famotidine 10 mg (p=0.192). For both the binary and the categorical analyses, patients who received famotidine 10 mg reported significantly more favorable global assessments than patients who received placebo (p<0.001).

4) The tables below show the proportion of patients reporting no awakenings with heartburn.

Proportion of Patients Reporting No Awakenings With Heartburn
All-Patients-Treated Approach (N=1221)

	Famotidine 20 mg (n=485)		Famotidine 10 mg (n=489)		Placebo (n=247)	
	n	(%)	n	(%)	n	(%)
No Awakenings	339	(69.9)	336	(68.7)	132	(53.4)
Any Awakenings	146	(30.1)	153	(31.3)	115	(46.6)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus famotidine 10 mg	1.07 (0.81, 1.41)	0.22	0.641
Famotidine 20 mg versus placebo	2.10 (1.52, 2.91)	20.33	<0.001
Famotidine 10 mg versus placebo	1.97 (1.43, 2.71)	17.07	<0.001

Adapted from electronic submission RefP117p.61

Medical Officer Comments: Significantly greater proportions of patients in both the

famotidine 20-mg and 10-mg groups reported no awakenings with heartburn compared to the placebo group (p<0.001 for both comparisons). There was no statistical difference between the two groups (20-mg vs. 10-mg) with regard to this parameter.

5) The tables below show the proportion of patients using rescue medication during the study

Proportion of Patients Using Rescue Medication During the Study
All-Patients-Treated Approach (N=1227)

	Famotidine 20 mg (n=488)		Famotidine 10 mg (n=490)		Placebo (n=249)	
	n	(%)	n	(%)	n	(%)
No Rescue	377	(77.3)	366	(74.7)	156	(62.7)
Any Rescue	111	(22.7)	124	(25.3)	93	(37.3)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus famotidine 10 mg	1.16 (0.86, 1.57)	0.98	0.323
Famotidine 20 mg versus placebo	2.08 (1.48, 2.92)	17.99	<0.001
Famotidine 10 mg versus placebo	1.79 (1.28, 2.50)	11.72	<0.001

Adapted from electronic submission RefP117p.62

Medical Officer Comments: The famotidine 20-mg and 10-mg groups were similar with respect to this parameter (p=0.323). A significantly greater proportion of patients in the placebo group used rescue medication compared to patients in the famotidine 20-mg (p<0.001) and famotidine 10-mg (p<0.001) groups.

Comparisons Summary of Efficacy

Summary of Efficacy Comparisons
All-Patients-Treated Approach

Efficacy Parameter	FAM 20 mg Versus FAM 10 mg	FAM 20 mg Versus Placebo	FAM 10 mg Versus Placebo
PRIMARY			
Peak heartburn during 3 hours postmeal	[P] 0.002 **	<0.001 **	<0.001 **
SECONDARY			
% Reporting no heartburn during 3 hours postmeal	0.006 **	<0.001 **	0.001 **
Mean heartburn severity during 3 hours postmeal	0.006 **	<0.001 **	0.007 **
Global assessment of efficacy measured at end of treatment period (all categories)	0.024 *	<0.001 **	<0.001 **
% Good/very good/excellent global assessment	0.192	<0.001 **	<0.001 **
% Reporting no awakenings with heartburn	0.641	<0.001 **	<0.001 **
% Using rescue medication during the study	0.323	<0.001 **	<0.001 **

[P] = Primary treatment comparison.
FAM = Famotidine.
* $p \leq 0.05$
** $p \leq 0.01$

Adapted from electronic submission RefP117p.63

The results of the interim analysis were generally consistent with the final results.

Subgroup Analysis

There was no evidence of a significant treatment-by-factor interaction (p>0.050) for either age, gender or race.

Peak Heartburn Severity During the 3 Hours Postmeal
By Age Group
All-Patients-Treated Approach (N=1227)

Treatment Group	Age Group	n	None	Mild	Moderate	Severe
			n (cum %)	n (cum %)	n (cum %)	n (cum %)
Famotidine 20 mg	65 or under	456	166 (36.4)	149 (69.1)	87 (88.2)	54 (100.0)
	Over 65	32	19 (59.4)	7 (81.3)	6 (100.0)	0 (100.0)
Famotidine 10 mg	65 or under	463	140 (30.2)	143 (61.1)	120 (87.0)	60 (100.0)
	Over 65	27	7 (25.9)	10 (63.0)	6 (85.2)	4 (100.0)
Placebo	65 or under	239	45 (18.8)	73 (49.4)	75 (80.8)	46 (100.0)
	Over 65	10	2 (20.0)	4 (60.0)	2 (80.0)	2 (100.0)

Adapted from electronic submission RefP117p396.

Medical Officer Comments: Less than 8% of the population in each group were ≥ 65 years old, the number is too small to do meaningful analysis.

Peak Heartburn Severity During the 3 Hours Postmeal
By Race
All-Patients-Treated Approach (N=1227)

Treatment Group	Race	n	None	Mild	Moderate	Severe
			n (cum %)	n (cum %)	n (cum %)	n (cum %)
Famotidine 20 mg	Caucasian	372	159 (42.7)	112 (72.8)	66 (90.6)	35 (100.0)
	Non-Caucasian	116	26 (22.4)	44 (60.3)	27 (83.6)	19 (100.0)
Famotidine 10 mg	Caucasian	366	126 (34.4)	109 (64.2)	87 (88.0)	44 (100.0)
	Non-Caucasian	124	21 (16.9)	44 (52.4)	39 (83.9)	20 (100.0)
Placebo	Caucasian	191	35 (18.3)	60 (49.7)	58 (80.1)	38 (100.0)
	Non-Caucasian	58	12 (20.7)	17 (50.0)	19 (82.8)	10 (100.0)

Adapted from electronic submission RefP117p396.

The test for the treatment-by-race interaction showed marginal significance (p=0.080). It appears that the interaction is being driven by the magnitude of the difference between placebo and the active treatments. The active treatment versus placebo differences are smaller for the non-Caucasian patients than for the Caucasian patients; the difference between the 2 active treatments is consistent for the race groups.

Safety

For safety evaluation, see Division of OTC's Medical Officer's Safety Review.
The safety of famotidine 20 mg was characterized by evaluating the incidence of clinical adverse experiences. There were no laboratory tests conducted for the evaluation of safety.

Discussion

Medical Officer Comments: Reference P117 is a single-dose study comparing famotidine 20 mg, famotidine 10 mg, and placebo in preventing heartburn symptoms when administered

10 minutes prior to a provocative meal. The majority of patients were Caucasians (75%), and the mean age was 42 years. There were more females than males (60% vs. 40%) for each treatment arm. Ninety-four percent of the patients in each treatment arm had heartburn for >12 months and majority had moderately severe to severe heartburn severity.

In this study, famotidine 20 mg was more effective than the 10 mg dose in reporting less severe peak heartburn symptoms, no heartburn symptoms (proportion of patients), and less severe mean heartburn symptoms. Further, famotidine 10 mg dose was better than placebo with regard to these previously mentioned parameters.

The famotidine 20-mg group had significantly more favorable global assessment compared to both the famotidine 10-mg and placebo groups; for the analysis of the proportion of patients reporting good, very good, or excellent global assessments, the comparison versus placebo was statistically significant, but not the comparison versus famotidine 10 mg. For both the binary and the categorical analyses, patients who received famotidine 10 mg reported significantly more favorable global assessments than patients who received placebo ($p<0.001$).

Significantly greater proportions of patients in both the famotidine 20-mg and 10-mg groups reported no awakenings with heartburn compared to the placebo group. There was no statistical difference between the two groups (20-mg vs. 10-mg) with regard to this parameter. A significantly greater proportion of patients in the placebo group used rescue medication compared to patients in the famotidine groups.

There was no evidence of a significant treatment-by-factor interaction ($p>0.050$) for either age, gender or race.

For details of safety assessment, please see the Agency's Division of Over-the-Counter Drugs Medical Officer's Review.

Appendix C

Reference P128
An In-Clinic, Randomized, Single-Dose, Double-Blind, Parallel Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered Prior to a Provocative Meal

Clinical Phase III

Study Period: April, 1999 to May, 1999

Hypotheses and Objectives

Hypotheses

Primary

- Patients dosed with famotidine 20 mg 10 minutes prior to a provocative meal will experience less severe heartburn than patients similarly dosed with famotidine 10 mg and similarly challenged, as measured by peak heartburn severity during the 3 hours following the start of the meal.

Secondary

- Compared to patients dosed with famotidine 10 mg 10 minutes prior to a provocative meal, patients similarly dosed with famotidine 20 mg and similarly challenged will experience less severe heartburn (as measured by mean heartburn severity during the 3 hours following the start of the meal) and will report more favorable global assessments of efficacy.
- Compared to patients dosed with placebo 10 minutes prior to a provocative meal, patients similarly dosed with famotidine 20 mg or famotidine 10 mg and similarly challenged will experience less severe heartburn during the 3-hour postmeal period (as measured by peak heartburn severity, mean heartburn severity, and proportion of patients with no heartburn) and will report more favorable global assessments of efficacy.

Primary Objective

To assess the ability of famotidine 20 mg and famotidine 10 mg to prevent heartburn in patients treated 10 minutes prior to an evening provocative meal.

Study Design

This was a multicenter, double-blind, double-dummy, randomized, parallel, single-dose study. Famotidine 20-mg FCT, Famotidine 10-mg FCT, and matching placebos were used as study medications. There were 1923 patients enrolled in the baseline run-in period to evaluate their heartburn over a 1-week period. To participate in the run-in period, patients had at least a 2-month history of food-induced heartburn occurring 3 or more times per week. Patients

experienced meal-induced heartburn that was frequently severe (≥30% of their episodes). The patients were given a 1-week, take-home diary card to confirm their eligibility for randomization into the double-blind treatment session. No study medication was provided. Patients satisfied all of the following criteria to be eligible to enter the treatment meal session:

- Had meal/beverage-induced heartburn, at least 3 times in the 1-week period, and at least 3 of the episodes were treated with antacid or H2 -receptor antagonists.
- At least 1 of their episodes during that 1-week period was considered severe (heartburn severity was determined by self-evaluation).
- Satisfactorily completed the diary card.

Eligible patients returned to the study facility no later than 15 days after returning their baseline diary cards for participation in the treatment meal session. During the treatment session, patients were required to remain at the study facility for a 4-hour period.

A total of 1334 patients were randomized to receive study drug. A total of 1330 patients completed the double-blind portion of the study. Patients were randomized to 3 treatment groups using a computer-generated schedule. During the treatment phase of the trial, qualified patients within each investigative site were randomized to 1 of 3 groups according to a randomization schedule.

- Famotidine 20-mg FCT/famotidine 10-mg matching placebo FCT
- Famotidine 10-mg FCT/famotidine 20-mg matching placebo FCT
- Famotidine 20-mg matching placebo FCT/famotidine 10-mg matching placebo FCT

Prior to the dose of study medication, the patient was assessed for the presence of heartburn. Patients were dismissed if heartburn was present prior to dosing. Ten minutes after the dose of study medication, patients consumed a provocative meal consisting of chili, cola, and a chocolate bar. The patients evaluated their heartburn symptoms at 30-minute intervals beginning 30 minutes after the start of the meal and continuing for 3 hours. Patients rated the severity of their heartburn using a 4-point scale.

Overall Study Flow Chart

Procedure	Visit 1	Visit 2†	Visit 3‡ Treatment Session
Medical history (including heartburn history)	X		
Evaluate inclusion/exclusion	X		
Informed consent	X		
Dispense diary card for run-in week	X		
Study medication (double blind)			X
Provocative meal			X
Complete diary card assessments (in-clinic)			X
Adverse experience monitoring		X	X
Prior/concomitant medications	X	X	X
Review patient diary card		X	X

† Visit occurred within 7 to 15 days of Visit 1.
‡ Visit occurred within 15 days of returning baseline diary card (Visit 2).

Adapted from electronic submission RefP128p.19

Concomitant Medications

- From 7 days prior to the treatment meal until they completed the study, the patients could not take prescription medications for gastrointestinal disease.
- Patients could not take lansoprazole or omeprazole 4 weeks prior to the treatment meal until study completion.
- Chronic use of nonsteroidal anti-inflammatory drugs, orally administered corticosteroids, anticholinergics, anticoagulants, tranquilizers, tricyclic antidepressants, or antineoplastics were prohibited.
- If other conditions emerged that required drug therapy during this study, those conditions and any concomitantly prescribed medication were recorded on the workbooks.

Rescue Medication

If patients used OTC H2-receptor antagonists for the relief of heartburn, they discontinued usage for 1 week prior to the treatment meal. The patient could replace with antacid usage up to 12 hours prior to the start of the study session.

Study Population

Inclusion Criteria

- Male or female patients who were at least 18 years of age or older who are cooperative, reliable, and of adequate intelligence to grade and record symptoms as requested.
- History of food-induced heartburn of at least 2 months duration with at least 3 episodes per week, and that was frequently severe (≥ 30% of their episodes). Patients were able to identify specific foods and beverages that produced symptoms and used antacids and/or OTC H 2 - receptor antagonists.
- Signed the informed consent after the nature of the study was fully explained and before any procedures dictated by this protocol were performed.
- Speak, read, and understand the English language in order to make heartburn assessments.

Exclusion Criteria

- History of a serious medical condition or evidence of impaired renal function.
- History of duodenal ulcer, gastric ulcer, atrophic gastritis, or diverticulitis within 2 years prior to study start; and a history of upper GASTROINTESTINAL tract surgery or vagotomy, esophageal strictures or Barrett's esophagus, endoscopically identified erosive esophagitis of moderate or greater severity, Zollinger-Ellison syndrome, irritable colon, inflammatory bowel disease, biliary tract disease, or known cholecystolithiasis.
- Pregnant or lactating. Women of childbearing potential used adequate means of contraception.
- Recently used (within 1 week of the treatment meal) or continued use of prescription medication which modified acid secretion. Used omeprazole or lansoprazole within the 4 weeks prior to the treatment meal. In addition, chronic use of nonsteroidal anti-inflammatory drugs, orally administered corticosteroids, anticholinergics, anticoagulants, tranquilizers, tricyclic antidepressants, or antineoplastics were prohibited.
- Recently used (within 1 week of the treatment meal) OTC H2 –receptor antagonists. If the patient used these for the relief of heartburn, the patient discontinued the usage for 1 week

prior to the treatment meal session and replaced with antacid usage up to (but not including) the day of the study session.

- Recent history of habituating drug or alcohol abuse, psychosis, or other condition making the patient unlikely to comply with the protocol.
- Used an investigational drug within 30 days prior to start of this study or within 5 half-lives of the investigational drug, whichever was longer.
- Previously participated in a heartburn study (within 3 months prior to study start).
- Prior adverse reaction to antacids, H2 -antagonists, any of the components of the study medication, or a prior adverse reaction to any ingredient(s) of the provocative meal.
- Other conditions that would interfere with data interpretation or create undue risk.

Medical Officer Comments: The inclusion and exclusion criteria appear adequate for the study.

Evaluation Criteria

Efficacy

- Heartburn symptoms: rated using the 3-point scale (1 = mild, 2 = moderate, 3 = severe) immediately before the dose of study medication was administered and at 30-minute intervals for the 3-hour period after the start of the treatment meal.
- Global assessment of treatment efficacy: at the end of the treatment session the patient rated the overall effect provided by the treatment. Patients were asked, "How do you feel the study medication worked?" and the Global Response was rated on the following scale Grade Rating (4 = Excellent, 3 = Very Good, 2 = Good, 1 = Fair, 0 = Poor)
- Rescue medication use: beginning 3 hours after the start of the provocative meal, patients could take rescue medication (MYLANTA™ Double Strength antacid; 2 tablets) and recorded for treatment of symptoms.

Safety Measurements

- Adverse experiences were monitored and recorded.
- Nonserious adverse experiences were monitored through 8 AM of the morning following the treatment meal.
- The investigator evaluated all adverse experiences as to:
  - Maximum intensity (mild, moderate, severe)
  - Seriousness
  - Relationship to the drug (definitely, probably, possibly, probably, probably *not* or definitely not related to test drug)

Statistical Planning and Analysis

The treatment groups were compared with respect to:

Primary Parameter:

(1) peak heartburn severity during the 3 hours following the start of the provocative meal.

Primary Comparison: The primary treatment comparison was famotidine 20 mg versus famotidine 10 mg for the primary parameter.

Secondary Parameters:

(2) The proportion of patients with no heartburn during the 3 hours following the start of the meal

(3) Mean heartburn severity during the 3 hours following the start of the meal

(4) Global assessment of efficacy measured at the end of the treatment period

(5) The proportion of patients who used rescue medication during the 3 hours following the start of the meal.

The proportion of patients who reported no heartburn symptoms during the 3 hours following the start of the meal was analyzed using a logistic regression model for binary data.

- Due to a very low incidence of rescue use, no statistical analysis was performed for the proportion of patients who used rescue medication during the 3 hours following the start of the meal.
- Mean heartburn severity during the 3 hours following the start of the meal was analyzed using an ANOVA model.

An all-patients-treated analysis was the primary approach used for the analysis of efficacy. A per-protocol approach was also used for the analysis of the primary efficacy parameter (peak heartburn severity). The all-patients-treated approach was used for the analysis of safety data. In the all-patients-treated approach, all patients who were randomized and received study medication were included, where data was available. In the per-protocol approach, serious protocol violators were identified prior to unblinding and were excluded.

Patients who took rescue medication at any time following the start of the meal were considered "treatment failures" for all time points subsequent to the use of rescue. Prior to analysis, all patients who were considered "treatment failures" were assigned severity scores of Severe for these time points, and a global assessment score of Poor.

Ethics

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Results

Patient Characteristics

Baseline Patient Characteristics by Treatment Group
All-Patients-Treated (N=1334)

	Famotidine 20 mg (n=532)	Famotidine 10 mg (n=537)	Placebo (n=265)	Total (N=1334)
Age (years)				
Mean	43.4	42.5	42.2	42.8
SD	13.5	13.4	12.4	13.2
Median	42.0	41.0	41.0	42.0
Range	18 to 77	19 to 82	19 to 81	18 to 82
N	532	537	265	1334
Gender				
Male	187 (35.2%)	189 (35.2%)	101 (38.1%)	477 (35.8%)
Female	345 (64.8%)	348 (64.8%)	164 (61.9%)	857 (64.2%)
Racial Origin				
Caucasian	422 (79.3%)	442(82.3%)	199 (75.1%)	1063 (79.7%)
Black	99 (18.6%)	82(15.3%)	55 (20.8%)	236 (17.7%)
Hispanic	8 (1.5%)	9 (1.7%)	9 (3.4%)	26 (1.9%)
Asian	0 (0.0%)	2 (0.4%)	0 (0.0%)	2 (0.1%)
Native American	0 (0.0%)	1 (0.2%)	1 (0.4%)	2 (0.1%)
American Indian	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Asian/Pacific Islander	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Bi-Racial	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.1%)
Korean	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Mixed	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Height (inches)				
Mean	67.0	66.8	67.0	66.9
SD	3.9	3.6	4.2	3.8
Median	66.5	66.0	66.0	66.0
Range	59 to 78	59 to 79	58 to 77	58 to 79
N	532	537	265	1334
Body Weight (lbs)				
Mean	185.6	185.9	187.4	186.1
SD	44.0	44.8	45.6	44.6
Median	180.0	180.0	180.0	180.0
Range	97 to 378	102 to 380	95 to 350	95 to 380
N	532	537	265	1334
Duration of Heartburn				
<2 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2 to 6 months	13 (2.4%)	9 (1.7%)	2 (0.8%)	24 (1.8%)
6 to 12 months	13 (2.4%)	11 (2.0%)	9 (3.4%)	33 (2.5%)
>12 months	506 (95.1%)	517 (96.3%)	254 (95.8%)	1277 (95.7%)
Typical Heartburn Severity				
Very mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Moderate	29 (5.5%)	33 (6.1%)	17 (6.4%)	79 (5.9%)
Moderately severe	357 (67.1%)	336 (62.6%)	164 (61.9%)	857 (64.2%)
Severe	126 (23.7%)	143 (26.6%)	77 (29.1%)	346 (25.9%)
Very severe	20 (3.8%)	24 (4.5%)	7 (2.6%)	51 (3.8%)

Adapted from electronic submission RefP128p.33-35

Medical Officer Comments: The majority of patients were Caucasians (75- 82%), and the mean age was 42 years with an age range of 18-82 years. There were more females than males (65% vs. 35%) for each treatment arm. Ninety-five percent of the patients in each treatment arm had heartburn for >12 months and majority of the patients had moderately severe to severe heartburn (90%). There were twice as many patients in each of the famotidine group compared to the placebo group. Baseline features were well-balanced across treatment arms.

The most frequently (incidence ≥2% in 1 or more treatment groups) reported secondary diagnosis by treatment group was headache. The majority of patients (≥76% in each treatment group) were on some sort of therapy prior to the time of enrollment and the most common prior drug therapy was calcium carbonate.

Patient Accounting

The table below shows an accounting for all randomized patients. A total of 1334 patients was randomized into the study and took study medication.

Patient Accounting for All Randomized Patients (N=1334)

	Famotidine 20 mg	Famotidine 10 mg	Placebo	Total
	n (%)	n (%)	n (%)	N (%)
Total randomized	532	537	265	1334
Completed study	529 (99.4)	536 (99.8)	265(100.0)	1330 (99.7)
Discontinued study	3 (0.6)	1 (0.2)	0 (0.0)	4 (0.3)
Clinical adverse experience	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)
Unbearably severe UGI symptoms	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.1)

Adapted from electronic submission RefP128p. 41

Medical Officer Comments: Two of the 1334 patients who were randomized were excluded from the all-patients-treated efficacy analyses. One ate a minimal amount of chili before vomiting during the treatment meal session and the other took an H2-receptor antagonist (PEPCID AC™) 35 minutes prior to dosing. All patients were included the safety analyses.

There were 31 (2.3%) patients who were considered major protocol violators; the percentages of patients were similar across treatment groups. These patients were excluded in the per-protocol approach. Six patients used rescue medication (famotidine 20-mg group=1, famotidine 10-mg group=2, and placebo group=3) and were considered "treatment failures".

Efficacy

The sponsor reported that there was no evidence of a treatment-by-investigator interaction ($p>0.050$) for any of the efficacy parameters, indicating that the treatment effect was consistent across investigator sites. Also, for the primary efficacy parameter (peak heartburn), there was no evidence of a treatment-by-factor interaction ($p>0.050$) for either age or gender.

The test for the treatment-by-race interaction was statistically significant (p=0.006). This interaction is being driven by the direction of the difference between placebo and the active treatments. The active treatment groups had more favorable responses than the placebo group for the Caucasian patients, whereas the opposite was true for the non-Caucasian patients; the difference between the 2 active treatments is consistent for the race groups.

Primary Parameter

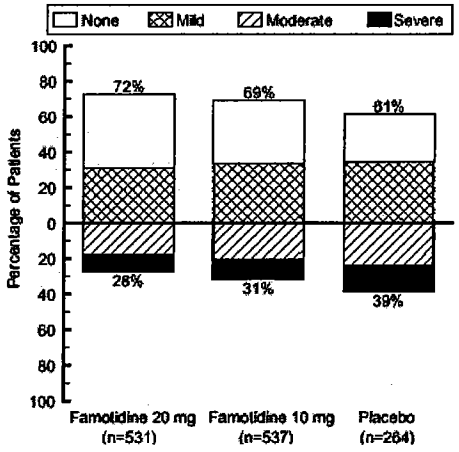
The tables below show the results of the peak heartburn severity during the 3 hours following the start of a provocative meal.

The difference between famotidine 20 mg and famotidine 10 mg was marginally significant (p=0.066). The patients in both the famotidine 20- and 10-mg groups had significantly less severe peak heartburn symptoms than the patients in the placebo group (p<0.001 and p=0.006, respectively).

***Peak* Heartburn Severity During the 3 Hours Postmeal**
All-Patients-Treated Approach (N=1332)

	Famotidine 20 mg (n=531)		Famotidine 10 mg (n=537)		Placebo (n=264)	
	n	(cum %)	n	(cum %)	n	(cum %)
None	219	(41.2)	190	(35.4)	71	(26.9)
Mild	165	(72.3)	178	(68.5)	90	(61.0)
Moderate	98	(90.8)	112	(89.4)	65	(85.6)
Severe	49	(100.0)	57	(100.0)	38	(100.0)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus famotidine 10 mg [P]	1.23 (0.99, 1.53)	3.38	0.066
Famotidine 20 mg versus placebo	1.79 (1.37, 2.35)	17.97	<0.001
Famotidine 10 mg versus placebo	1.46 (1.12, 1.91)	7.61	0.006
[P] = Primary treatment comparison.			



Adapted from electronic submission RefP128p. 46-47

Medical Officer Comments: The results above show that the patients in both the famotidine groups had significantly less severe peak heartburn symptoms compared to the placebo group (p<0.001 and p=0.006, respectively). The difference between famotidine 20 mg and famotidine 10 mg was marginally significant (p=0.066). The odds-ratios indicate that famotidine 20-mg patients were 1.23 and 1.79 times more likely to report less severe peak symptoms than famotidine 10-mg and placebo patients, respectively.

Secondary Parameters

1) The tables below show the proportion of patients reporting no heartburn symptoms during the 3 hours postmeal.

Proportion of Patients Reporting No Heartburn Symptoms During the 3 Hours Postmeal

All-Patients-Treated Approach (N=1332)

	Famotidine 20 mg (n=531)		Famotidine 10 mg (n=537)		Placebo (n=264)	
	n	(%)	n	(%)	n	(%)
No Heartburn	219	(41.2)	190	(35.4)	71	(26.9)
Any Heartburn	312	(58.8)	347	(64.6)	193	(73.1)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus famotidine 10 mg	1.29 (1.00, 1.66)	3.95	0.047
Famotidine 20 mg versus placebo	1.93 (1.39, 2.68)	15.41	<0.001
Famotidine 10 mg versus placebo	1.49 (1.07, 2.08)	5.68	0.017

Adapted from electronic submission RefP128p.48

Medical Officer Comments: The results show that there was a greater percentage of patients reporting no heartburn symptoms in the famotidine 20-mg group than in both the famotidine 10-mg (p=0.047) and the placebo (p<0.001) groups. The famotidine 10-mg group had a greater percentage of patients with no heartburn than the placebo group (p=0.017).

2) The tables below displays the results of the mean heartburn severity during the 3-hour postmeal period.

Mean Heartburn Severity During the 3 Hours Postmeal

All-Patients-Treated Approach (N=1332)

Treatment Group	n	Mean†	Standard Error
Famotidine 20 mg	531	0.49	0.028
Famotidine 10 mg	537	0.52	0.028
Placebo	264	0.63	0.039

† 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe

Treatment Comparison	Mean Difference (95% CI)	F-Statistic	p-Value
Famotidine 20 mg versus famotidine 10 mg	-0.03 (-0.10, 0.05)	0.44	0.509
Famotidine 20 mg versus placebo	-0.14 (-0.23, -0.05)	8.72	0.003
Famotidine 10 mg versus placebo	-0.11 (-0.21, -0.02)	5.86	0.016

Adapted from electronic submission RefP128p.49

Medical Officer Comments: Both famotidine groups (20mg & 10mg) reported less severe mean heartburn symptoms compared to placebo (p=0.003 and p=0.016, respectively). There was no statistical difference between the two famotidine groups.

3) Below are the tables and figures showing the global assessment of efficacy measured at the end of the treatment period.

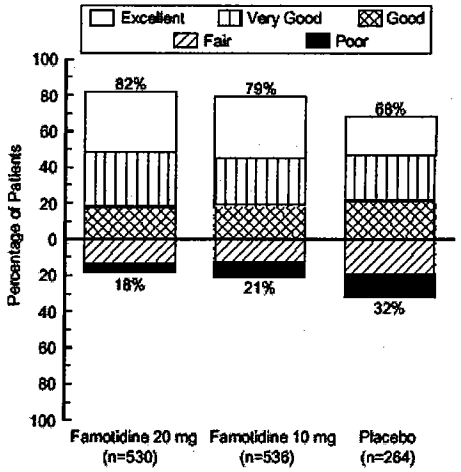
Global Assessment of Efficacy

All-Patients-Treated Approach (N=1330)

	Famotidine 20 mg (n=530)		Famotidine 10 mg (n=536)		Placebo (n=264)	
	n	(cum %)	n	(cum %)	n	(cum %)
Excellent	176	(33.2)	181	(33.8)	57	(21.6)
Very Good	160	(63.4)	142	(60.3)	66	(46.6)
Good	96	(81.5)	101	(79.1)	57	(68.2)
Fair	73	(95.3)	68	(91.8)	52	(87.9)
Poor	25	(100.0)	44	(100.0)	32	(100.0)

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Proportion of Patients Reporting Good, Very Good, or Excellent			
Famotidine 20 mg versus famotidine 10 mg	1.17 (0.86, 1.58)	0.97	0.324
Famotidine 20 mg versus placebo	2.07 (1.47, 2.91)	17.24	<0.001
Famotidine 10 mg versus placebo	1.77 (1.27, 2.48)	11.17	<0.001
All Categories			
Famotidine 20 mg versus famotidine 10 mg	1.08 (0.87, 1.35)	0.52	0.471
Famotidine 20 mg versus placebo	1.96 (1.50, 2.55)	24.48	<0.001
Famotidine 10 mg versus placebo	1.81 (1.39, 2.35)	19.17	<0.001

Adapted from electronic submission RefP128p.52



Adapted from electronic submission RefP128p. 52-53

Medical Officer Comments: Both famotidine groups reported significantly more favorable global assessments compared to placebo group (p<0.001 for both). The difference between the famotidine 20 mg and famotidine 10 mg group was not statistically significant for either the binary (p=0.324) or the categorical (p=0.471) analysis.

Summary of Efficacy Comparisons
All-Patients-Treated Approach

Efficacy Parameter	FAM 20 mg Versus FAM 10 mg	FAM 20 mg Versus Placebo	FAM 10 mg Versus Placebo
PRIMARY			
Peak heartburn during 3 hours postmeal	[P] 0.066 +	<0.001 **	0.006 **
SECONDARY			
% Reporting no heartburn during 3 hours postmeal	0.047 *	<0.001 **	0.017 *
Mean heartburn severity during 3 hours postmeal	0.509	0.003 **	0.016 *
Global assessment of efficacy measured at end of treatment period (all categories)	0.471	<0.001 **	<0.001 **
% Good/very good/excellent global assessment	0.324	<0.001 **	<0.001 **
[P] = Primary treatment comparison. FAM = Famotidine. + 0.05<p≤0.10; * p≤0.05; ** p≤0.01			

Adapted from electronic submission RefP128p.54

Subgroup Analysis

In this study, the test for the treatment-by- race interaction was statistically significant (p=0.006). The active treatment groups had more favorable responses than the placebo group for the Caucasian patients, the response of the non-Caucasian (Black, Hispanic, and "other" groups) was the opposite. It appears that the interpretation of this finding is confounded by the potential differences in response by site as the majority (76%) of the non-Caucasian patients were enrolled at 6 of the 15 investigator sites. This finding is unlikely to have been responsible for the absence of a statistically significant difference in the primary endpoint. See tables below.

Peak Heartburn Severity During the 3 Hours Postmeal
By Age Group
All-Patients-Treated Approach (N=1332)

Treatment Group	Age Group	n	None n (cum %)	Mild n (cum %)	Moderate n (cum %)	Severe n (cum %)
Famotidine 20 mg	65 or under	494	204 (41.3)	155 (72.7)	89 (90.7)	46 (100.0)
	Over 65	37	15 (40.5)	10 (67.6)	9 (91.9)	3 (100.0)
Famotidine 10 mg	65 or under	503	177 (35.2)	165 (68.0)	107 (89.3)	54 (100.0)
	Over 65	34	13 (38.2)	13 (76.5)	5 (91.2)	3 (100.0)
Placebo	65 or under	253	68 (26.9)	88 (61.7)	62 (86.2)	35 (100.0)
	Over 65	11	3 (27.3)	2 (45.5)	3 (72.7)	3 (100.0)

Adapted from electronic submission RefP128p.463

Medical Officer Comments: Less than 8% of the population in each group were ≥ 65 years old, the number is too small to do meaningful analysis.

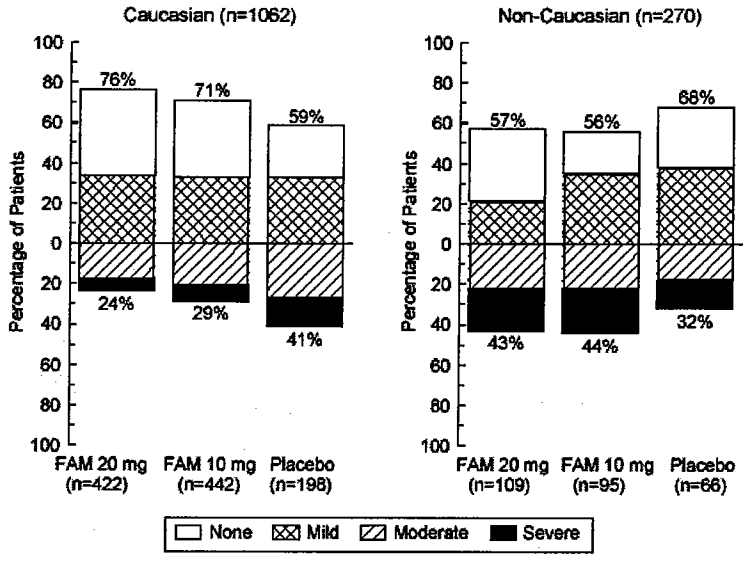
Peak Heartburn Severity During the 3 Hours Postmeal
By Race
All-Patients-Treated Approach (N=1332)

Treatment Group	Race	n	None	Mild	Moderate	Severe
			n (cum %)	n (cum %)	n (cum %)	n (cum %)
Famotidine 20 mg	Caucasian	422	180 (42.7)	142 (76.3)	74 (93.8)	26 (100.0)
	Non-Caucasian	109	39 (35.8)	23 (56.9)	24 (78.9)	23 (100.0)
Famotidine 10 mg	Caucasian	442	170 (38.5)	145 (71.3)	91 (91.9)	36 (100.0)
	Non-Caucasian	95	20 (21.1)	33 (55.8)	21 (77.9)	21 (100.0)
Placebo	Caucasian	198	51 (25.8)	65 (58.6)	53 (85.4)	29 (100.0)
	Non-Caucasian	66	20 (30.3)	25 (68.2)	12 (86.4)	9 (100.0)

Adapted from electronic submission RefP128p.581

The test for the treatment-by-race (Caucasians vs. non-Caucasians) interaction was statistically significant (p=0.006). The active treatment groups had more favorable responses than the placebo group for the Caucasian patients, whereas the opposite was
true for the non-Caucasian patients; the difference between the 2 active treatments is consistent for the race groups.

Peak Heartburn Severity During the 3 Hours Postmeal
By Race
All-Patients-Treated Approach (N=1332)
Percentage of Patients



Adapted from electronic submission Appendix 4.1.9 p. 465

Safety

For safety evaluation, please see OTC medical Officer's Safety Review.

Discussion

Medical Officer Comments: Reference P128 is a single dose study comparing famotidine 20mg, famotidine 20mg and placebo in preventing heartburn symptoms when administered 10 minutes prior to a provocative meal. The majority of patients were Caucasians (75-82%), and the mean age was 42 years with an age range of 18-82 years. There were more females than males (65% vs. 35%) for each treatment arm. Ninety-five percent of the patients in each treatment arm had heartburn for >12 months and majority of the patients had moderately severe to severe heartburn (90% combined). There were twice as many patients in each of the famotidine group compared to the placebo group. Baseline features were well balanced across treatment arms.

In this study, there was a greater percentage of patients reporting no heartburn symptoms in the famotidine 20-mg group than in both the famotidine 10-mg and the placebo groups. The famotidine 10-mg group had a greater percentage of patients with no heartburn symptoms compared to the placebo group.

Both famotidine groups (20mg & 10mg) reported less severe mean heartburn symptoms during the 3 hours postmeal compared to the placebo group. There was no statistical difference between the two famotidine groups.

Both the famotidine groups experienced less severe peak heartburn symptoms compared to the placebo group, however, the difference between famotidine 20 mg and famotidine 10 mg was marginally significant (p=0.066). The odds-ratios indicate that famotidine 20-mg patients were 1.23 and 1.79 times more likely to report less severe peak symptoms than famotidine 10-mg and placebo patients, respectively.

Both famotidine groups reported significantly more favorable global assessments compared to placebo group. The difference between the famotidine 20 mg and famotidine 10 mg group was not statistically significant for either the binary (p=0.324) or the categorical (p=0.471) analysis.

For this study, the test for treatment-by-race interaction was significant (p=0.006); the active treatment groups had more favorable responses than the placebo group for the Caucasian patients, the response of the non-Caucasian (Black, Hispanic, and "other" groups) was the opposite. It appears that the interpretation of this finding is confounded by the potential differences in response by site as the majority (76%) of the non-Caucasian patients were enrolled at 6 of the 15 investigator sites. This finding is unlikely to have been responsible for the absence of a statistically significant difference in the primary endpoint.

For details of safety assessment, please see the Agency's Division of Over-the-Counter Drugs Medical Officer's Review.

Appendix D

Protocol 017 (P017)

A Double-Blind, Dose Ranging Study to Evaluate the Effects of Doses as Needed up to Twice Daily of Famotidine 5 mg, 10 mg, 20 mg, or Antacid, as Compared to Placebo in the Treatment of Intermittent Heartburn

Clinical Phase III

Study Period: October, 1989 to November, 1990

Hypotheses and Objectives

Hypotheses

- Famotidine 5 mg, 10 mg and 20 mg, will relieve heartburn faster and more frequently than placebo.
- Antacid will relieve heartburn more frequently than placebo.
- No significant deleterious changes in gastrointestinal mucosa integrity will occur after 4 weeks prn famotidine, antacid, or placebo use.
- No significant deleterious changes in gastrointestinal mucosa integrity will occur in patients with questionable or abnormal esophageal motility at study entry, after 4 weeks prn famotidine, antacid, or placebo.

Objectives

- To identify a dose for Phase III testing by assessing the efficacy of famotidine vs. placebo in relief of heartburn.
- To assess the efficacy of antacid vs. placebo in relief of heartburn.
- To assess whether underlying diseases, if any, of the gastrointestinal tract in patients with heartburn are affected by prn famotidine or antacid by performing pre- and post treatment upper gastrointestinal endoscopy in heartburn patients.
- To estimate the prevalence of esophageal motility disorders, and to assess whether prn famotidine or antacids affect patients with questionable or abnormal esophageal motility.

Study Design

This was a multicenter, randomized, double-blind, parallel, placebo-controlled, at-home, multiple-episode treatment of heartburn trial. This study was conducted using 29 investigator sites, which used famotidine 20 mg, famotidine 10 mg, antacid, famotidine 5 mg and placebo as study medications.

The study was conducted in two phases: a one-week, single-blind baseline phase followed by a four week double blind phase. For the baseline phase, patients with a history of heartburn requiring self-medication with antacid 3 or more times a week participated in a 1-week, single-blind, at-home evaluation during which when they developed heartburn, they recorded the initial severity of the episode on a diary card using a 4-point scale (Mild, Moderate, Severe, Very

Severe). At hourly intervals following dosing for treatment of heartburn, patients recorded their response to study the medication (single-blind antacid) using a 4-point scale:

- Completely Relieved (gone)
- Better (noticeably improved)
- Unchanged (not much different)
- Worse (more severe)

Those who qualified for randomization into the double-blind phase were the patients that reported at least 3 episodes of heartburn improved within 1 hour by self-medication with single-blind antacid. For the double-blind phase, the coded test medications were randomly assigned and assigned in a double-dummy fashion. There were 5 treatment groups:

Group I ***Placebo***	Placebo antacid tablets and placebo famotidine tablets prn for heartburn up to twice daily
Group II ***Famotidine 5mg***	Placebo antacid tablets and 5 mg famotidine tablets prn for heartburn up to twice daily
Group III ***Famotidine 10mg***	Placebo antacid tablets and 10 mg famotidine tablets prn for heartburn up to twice daily
Group IV ***Famotidine 20mg***	Placebo antacid tablets and 20 mg famotidine tablets prn for heartburn up to twice daily
Group V ***Antacid***	Active antacid tablets placebo famotidine tablets prn for heartburn up to twice daily

Randomized patients received at-home diary cards to record episodes of heartburn for a total of 4 weeks. Patients initially received test medication for 14 days,
(28 famotidine/famotidine placebo tablets and 28 antacid/antacid placebo tablets). A second diary card and test medication for an additional 14 days was distributed on the 14th day.

Before dosing for each episode of heartburn, patients recorded the initial severity (Mild, Moderate, Severe, Very Severe) of the episode on the diary. At hourly intervals following dosing for treatment of heartburn, patients recorded whether their heartburn was completely relieved, better, unchanged, or worse, as compared to the severity of heartburn at the time of dosing assessed each dose of test medication hourly for 3 hours.

If the test medication was ineffective exhausted, or if heartburn occurred and both doses of test medication for that day were taken, patients were given rescue medication (open-label antacid) to use. Patients were permitted to take up to two doses of test medication in one day (6:00 am to 6:00 am).

Clinical and Laboratory Measurements

1. Clinical	Visit 1	Day 0	Day 14	Day 28
History	X			
Complete Physical Exam	X			X
Interval History		X	X	X
Interval Physical Exam		X	X	
Adverse Reactions		X	X	X
Medication Counted		X	X	X
Diary Reviewed	X	X	X	X
Patient's Global Assessment				X

2. Laboratory	Visit 1	Day 0	Day 14	Day 28
A. Hematology				
Hemoglobin	X			X
Hematocrit	X			X
WBC	X			X
Differential	X			X
Platelet Count	X			X
B. Chemistry				
ALT (SGPT)	X			X
AST (SGOT)	X			X
Alkaline Phosphatase	X			X
Total Bilirubin	X			X
Creatinine	X			X
BUN	X			X

3. Special Tests (Patient must Fast [NPO])				
Upper Gastrointestinal Endoscopy		X		X
Esophageal Motility		X		X*

*Performed only if Day 0 recording was questionable or abnormal.

Concomitant Medications

- Concurrent therapy with any H_2-receptor antagonists, sucralfate, misoprostol or omeprazole was not allowed.
- Chronically administered medications for the treatment of secondary illnesses were allowed.
- Any medications taken by the patient were recorded on the case report form.
- No specific diet was prescribed during the study.

Study Population

Inclusion Criteria

- Males or females, age of 18 years or legal age of consent.
- Females of child-bearing potential had to be using, planned to continue using, a reliable means of contraception.
- A history of heartburn which required self-medication with antacid 3 or more times a week.
- Willing to participate in the study and undergo endoscopy twice and esophageal motility recording once and possibly twice.
- Willing to and able to complete a symptom diary.

Exclusion Criteria

- Less than 18 years old.
- Medically significant concurrent disease.
- Pregnant, lactating or of childbearing potential who were not using a reliable means of contraception.
- Inability to comply with the protocol due to concomitant psychiatric or medical condition.
- Presently with or within the preceding one month of enrollment, unstable heart disease.
- Any contraindication to upper gastrointestinal endoscopy or upper gastrointestinal motility study.
- Treatment of investigational drugs within one month prior to the study.
- Any other conditions which would have precluded the patient's participation in the study, in the investigator's opinion.
- Hypersensitivity to any component of these medications.
- Patients expected to require other H_2-receptor antagonists, sucralfate, misoprostol or omeprazole.

Evaluation Criteria

Efficacy

- Response to therapy: response to test medication were recorded at 1, 2, 3 hours postdose during baseline; ½ hour, 1 hour, 1-½ hours, 2 hours and 3 hours postdose for the first double blind heartburn episode; and 1, 2, and 3 hours postdose for all remaining episodes of heartburn. The therapy scale completed the following statement: "Compared to when I took the test medication, my heartburn is: completely relieved, better, unchanged, or worse." The total number of back-up medication and the number of heartburn episodes experienced that day were recorded.
- Global assessment: at the conclusion of the study, patients rated their overall response: "How did your heartburn respond to test medication?" (excellent, good, fair poor or none).

Safety

- Adverse experience reporting: adverse experiences were monitored and recorded; and evaluated as to maximum intensity (mild, moderate, severe); seriousness; and relationship to the drug.
- Endoscopy: performed prior to entry to the double blind phase and at the study conclusion to assess whether there was mucosal disease. Esophagitis noted by the endoscopist was classified (grade 0 to 4).
- Esophageal motility: obtained prior to entry to the double blind phase and at the study conclusion, in patients with a questionable or abnormal recording at baseline.

Statistical Planning and Analysis

The data was analyzed to determine if the treatment groups differ with respect to the:

- number of episodes requiring self-medication occurring during the 4-week study
- patients global evaluation of the test drug upon completion of the study
- time onset of heartburn relief (looking specifically at a patient's first episode)
- proportion of episodes completely relieved of heartburn symptoms
- proportion of episodes requiring antacid rescue medication
- proportion of episodes requiring remedication

Global evaluation, proportion of episodes relieved, proportion of episodes requiring back-up medication and proportion of episodes requiring remedication by logistic regression using SAS, PROC LOGISTIC; the model included terms for treatment, investigator, baseline episode severity, and baseline number of episodes. Number of heartburn episodes: likelihood ratio test based on Poisson distribution. Time to relief of first episode by survival analysis using SAS, PROC PHGLM; the model included terms of treatment, investigator, and initial episode severity. A sample size of n=85 patients per group has 80% power to detect a 25% difference in proportion of episodes relieved between placebo and active treatment (at α=0.05, two tailed).

For inclusion/exclusion of data: patients were excluded from the "per-protocol analyses" for two reasons:

- patient took concomitant H2-receptor antagonist during the double blind phase
- less than 3 episodes of heartburn improved within an hour

Ethics

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Results

Patient Characteristics

Baseline Patient Characteristics by Treatment Group
All Randomized Patients (N=565)

	Famotidine 20 mg (n=115)	Famotidine 10 mg (n=113)	Famotidine 5 mg (n=113)	Antacid (n=113)	Placebo (n=111)	Total (n=565)
Age (years)						
Mean	43.7	43.5	44.7	45.3	43.3	44.1
SD	13.9	12.9	13.3	13.1	13.5	13.3
Median	41.0	42.0	42.0	44.0	41.0	42.0
Range	21 to 77	18 to 77	20 to 81	21 to 74	19 to 73	18 to 81
N	115	113	113	113	111	565
Gender						
Male	68(59.1%)	56(49.6%)	66(58.4%)	56(49.6%)	60(54.1%)	306(54.2%)
Female	47(40.9%)	57(50.4%)	47(41.6%)	57(50.4%)	51(45.9%)	259(45.8%)
Racial Origin						
Caucasian	102(88.7%)	103(91.2%)	101(89.4%)	100(88.5%)	97(87.4%)	503(89.0%)
Black	10 (8.7%)	8 (7.1%)	7 (6.2%)	7 (6.2%)	10 (9.0%)	42 (7.4%)
Hispanic	2 (1.7%)	1 (0.9%)	4 (3.5%)	4 (3.5%)	2 (1.8%)	13 (2.3%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.2%)
Chinese	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.2%)
East Indian	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hawaiian	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.2%)
Indian	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Oriental	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.2%)
Frequency of Heartburn						
Daily	99(86.1%)	90(79.6%)	84(74.3%)	84(74.3%)	94(84.7%)	451(79.8%)
Weekly	16(13.9%)	23(20.4%)	29(25.7%)	29(25.7%)	17(15.3%)	114(20.2%)

Adapted from electronic submission RefP017p. 25

Medical Officer Comments: The majority of patients were Caucasians (89%), and the mean age was 44 years old with an age range of 18 to 81 years. There were slightly more males than females (54% vs. 46%) and most patients in the study had daily heartburn. Baseline features were generally well balanced across treatment groups.

Patient Accounting

Patient Accounting for All Randomized Patients (N=565)

	Famotidine 20 mg		Famotidine 10 mg		Famotidine 5 mg		Antacid		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total randomized	115		113		113		113		111		565	
Completed study	110	(95.7)	106	(93.8)	108	(95.6)	104	(92.0)	102	(91.9)	530	(93.8)
Discontinued study	5	(4.3)	7	(6.2)	5	(4.4)	9	(8.0)	9	(8.1)	35	(6.2)
Clinical adverse experience	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.9)	2	(1.8)	4	(0.7)
Lost to follow-up	1	(0.9)	3	(2.7)	0	(0.0)	2	(1.8)	0	(0.0)	6	(1.1)
Protocol deviation	1	(0.9)	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.9)	3	(0.5)
No therapeutic response	1	(0.9)	1	(0.9)	0	(0.0)	2	(1.8)	1	(0.9)	5	(0.9)
Patient uncooperative	2	(1.7)	2	(1.8)	3	(2.7)	3	(2.7)	5	(4.5)	15	(2.7)
Motility not tolerated	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.2)
Treatment of new condition	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	1	(0.2)

Adapted from electronic submission RefP017p 27

Medical Officer Comments: For the baseline phase of the study, a total of 792 patients were enrolled, of these, 227 did not continue into the double-blind randomized phase. Failure to experience at least 3 episodes of heartburn that responded to antacid was the most frequent reason for not qualifying into the double-blind phase. There were 565 patients randomized into the double-blind phase, but only 530 (~94%) patients completed the study.

Efficacy

Global Evaluations

At the end of the 28-day double blind treatment period, patients globally assessed their response to treatment (excellent, good, fair, poor, none).

Global Evaluations
Per-Protocol Analysis

	Placebo (N=93)		Antacid (N=94)		FAM 5 mg (N=94)		FAM 10 mg (N=91)		FAM 20 mg (N=103)	
	n	(Cum %)	n	(Cum %)	n	(Cum %)	n	(Cum %)	n	(Cum %)
Excellent	12	(13%)	13	(14%)	21	(22%)	16	(18%)	24	(23%)
Good	44	(60%)	52	(69%)	44	(69%)	51	(74%)	53	(75%)
Fair	26	(88%)	24	(95%)	23	(94%)	17	(92%)	21	(95%)
Poor	9	(98%)	4	(99%)	6	(100%)	5	(98%)	3	(98%)
None	2	(100%)	1	(100%)	0	(100%)	2	(100%)	2	(100%)

Treatment Effect	Odds-Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	1.43	0.83, 2.46	1.62	0.2031
Placebo vs. 5 mg	1.80	1.04, 3.12	4.38	0.0365
Placebo vs. 10 mg	1.76	1.01, 3.05	3.99	0.0457
Placebo vs. 20 mg	2.20	1.28, 3.79	8.20	0.0042
Antacid vs. 5 mg	1.26	0.73, 2.18	0.70	0.4034
Antacid vs. 10 mg	1.23	0.71, 2.14	0.55	0.4577
Antacid vs. 20 mg	1.55	0.90, 2.65	2.53	0.1116
5 mg vs. 10 mg	0.98	0.56, 1.70	0.01	0.9315
5 mg vs. 20 mg	1.22	0.72, 2.09	0.55	0.4595
10 mg vs. 20 mg	1.25	0.73, 2.16	0.67	0.4118

Adapted from electronic submission RefP017p.55

2-sided p-Values for Comparisons of Global Effect

	Per Protocol	ITT
Antacid vs. Placebo	0.2031	0.4323
Famotidine 5 mg vs. Placebo	0.0365	0.0957
Famotidine 10 mg vs. Placebo	0.0457	0.1166
Famotidine 20 mg vs. Placebo	0.0042	0.0291

Medical Officer Comments: In the per protocol analysis, each of the famotidine group appear to be superior compared to placebo (p=0.0042), however, there were no significant differences among the famotidine groups. For the intent-to-treat analysis, only the famotidine 20 mg was statistically superior to placebo.

Number of Heartburn Episodes

Patients were allowed to self-medicate as needed for heartburn, up to twice daily during the study. The number of heartburn episodes was analyzed to determine whether active treatment reduced the total number of heartburn episodes over the course of the double blind treatment period.

14-Day Episode Rates
(Per-Protocol Analysis)
Treated episodes

Treatment Group	Weeks 1 and 2 Rate	Weeks 1 and 2 S.E.	Weeks 3 and 4 Rate	Weeks 3 and 4 S.E.	Full Study Rate	Full Study S.E.
Placebo	12.12	0.35	11.40	0.35	11.03	0.23
Antacid	12.18	0.35	11.15	0.34	11.16	0.23
Famotidine 5 mg	12.37	0.36	11.71	0.35	11.17	0.23
Famotidine 10 mg	12.36	0.36	12.07	0.36	11.39	0.24
Famotidine 20 mg	11.86	0.34	11.16	0.33	10.95	0.22

Treatment Effect	Weeks 1 and 2 Chi-Square	Weeks 1 and 2 p-Value	Weeks 3 and 4 Chi-Square	Weeks 3 and 4 p-Value	Full Study Chi-Square	Full Study p-Value
Placebo vs. Antacid	0.02	0.8977	0.27	0.6063	0.16	0.6897
Placebo vs. 5 mg	0.25	0.6170	0.38	0.5378	0.17	0.6838
Placebo vs. 10 mg	0.22	0.6392	1.76	0.1848	1.18	0.2778
Placebo vs. 20 mg	0.28	0.5939	0.26	0.6133	0.07	0.7891
Antacid vs. 5 mg	0.14	0.7086	1.29	0.2554	0.00	0.9944
Antacid vs. 10 mg	0.12	0.7311	3.40	0.0650	0.48	0.4891
Antacid vs. 20 mg	0.44	0.5050	0.00	0.9833	0.46	0.4989
5 mg vs. 10 mg	0.00	0.9796	0.52	0.4711	0.47	0.4923
5 mg vs. 20 mg	1.09	0.2968	1.30	0.2541	0.47	0.4932
10 mg vs. 20 mg	1.01	0.3150	3.47	0.0625	1.89	0.1694

Adapted from electronic submission RefP017p. 58

Medical Officer Comments: The above results shows that there were no differences among treatment groups in the analysis of the number of treated heartburn episodes.

Proportion of Heartburn Episodes Completely Relieved

Patients were allowed to self-medicate for heartburn as needed up to twice daily during the 4-week treatment study. Patients took one dose of "test medication" and then record their response; 1 hour later, if "complete relief" has not occurred, a "back-up medication" can be taken (an open-label antacid). Three hours later, if complete relief has not occurred, they were permitted to take a second dose of "test medication". The proportion of episodes successfully treated by test medication during the 4-week treatment was determined to analyze the data.

Median Proportion of Episodes Relieved
(Per-Protocol Analysis)
Treated Episodes

Placebo (n=96)	Antacid (n=99)	FAM 5 mg (n=97)	FAM 10 mg (n=94)	FAM 20 mg (n=105)
0.43	0.63	0.61	0.71	0.70

Adapted from electronic submission RefP017p. 64

Proportion of Episodes Relieved
(Per-Protocol Analysis)

Category	Placebo (N=96)		Antacid (N=99)		FAM 5 mg (N=97)		FAM 10 mg (N=94)		FAM 20 mg (N=105)	
	n	(Cum %)	n	(Cum %)	n	(Cum %)	n	(Cum %)	n	(Cum %)
All Relieved	9	(9%)	6	(6%)	7	(7%)	10	(11%)	18	(17%)
2/3 to All	18	(28%)	33	(39%)	31	(39%)	43	(56%)	39	(54%)
1/3 to 2/3	34	(64%)	39	(79%)	36	(76%)	22	(80%)	25	(78%)
0 to 1/3	25	(90%)	19	(98%)	16	(93%)	14	(95%)	18	(95%)
None Relieved	10	(100%)	2	(100%)	7	(100%)	5	(100%)	5	(100%)

Treatment Effect	Odds-Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	1.80	1.07, 3.02	4.93	0.0264
Placebo vs. 5 mg	1.70	1.01, 2.86	3.97	0.0464
Placebo vs. 10 mg	2.83	1.67, 4.80	14.88	0.0001
Placebo vs. 20 mg	3.08	1.83, 5.17	18.05	0.0001
Antacid vs. 5 mg	0.94	0.56, 1.58	0.05	0.8256
Antacid vs. 10 mg	1.57	0.93, 2.65	2.89	0.0892
Antacid vs. 20 mg	1.71	1.03, 2.84	4.30	0.0382
5 mg vs. 10 mg	1.67	0.99, 2.82	3.64	0.0565
5 mg vs. 20 mg	1.81	1.09, 3.02	5.21	0.0224
10 mg vs. 20 mg	1.09	0.65, 1.82	0.10	0.7471

Adapted from electronic submission RefP017p. 66

Medical Officer Comments: The analysis of the above data demonstrated that famotidine 20 mg is significantly superior to placebo, antacid and famotidine 5 mg (p=0.001, p=0.0382 and p=0.0224, respectively). In general, patients in the famotidine and antacid groups had a greater proportion of heartburn episodes relieved compared to those in the placebo group. The famotidine 20 mg and 10 mg groups appear to have more favorable results than the antacid and placebo groups. The "intent-to-treat" analysis results were similar to the "per protocol" analysis results except that the difference between famotidine 5 mg and placebo was marginal (p=0.065), and famotidine 10 mg was did not appear to be superior to famotidine 5 mg and antacid.

Complete Relief Within 1 Hour of Dosing

Complete Relief Within 1 Hour of Dosing
Efficacy Population (N=552)

Treatment Group	N	Total Heartburn Episodes	Model-Adjusted Probability of Complete Relief Within 1 Hour
Famotidine 20 mg	113	2664	0.379
Famotidine 10 mg	109	2642	0.344
Famotidine 5 mg	110	2612	0.307
Antacid	112	2559	0.296
Placebo	108	2534	0.235

N = Number of patients.

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus placebo	1.98 (1.38, 2.86)	13.49	<0.001
Famotidine 10 mg versus placebo	1.70 (1.18, 2.45)	8.28	0.004
Famotidine 20 mg versus famotidine 10 mg	1.17 (0.82, 1.67)	0.71	0.400

Adapted from electronic submission RefP017p.30,Ref.2

Medical Officer Comments: The tables above demonstrate that the famotidine 20 mg and 10 mg groups had greater proportion of heartburn episodes relieved within 1 hour of dosing as compared to the placebo group ($p<0.001$ and $p<0.004$, respectively). In addition, the famotidine 20 mg group appear to have a numerically greater probability of complete heartburn relief (0.379); and the model-adjusted odds-ratio indicate that patients in this group were 1.17 and 1.98 times more likely to report complete relief compared to those in the 10 mg and placebo groups.

Proportion of Heartburn Episodes Requiring Back-up Medication

Patients took back-up medication (an open-label antacid) if heartburn persisted 1-hour after a dose of test medication. The proportion of episodes for which a patient took bac-up medication was determined to analyze the data.

Median Proportion of Episodes Requiring Back-up Medication
(Per-Protocol Analysis)
Treated Episodes

Placebo (n=96)	Antacid (n=99)	FAM 5 mg (n=97)	FAM 10 mg (n=94)	FAM 20 mg (n=105)
0.41	0.32	0.33	0.22	0.25

Adapted from electronic submission RefP017p.72

Proportion of Heartburn Episodes Requiring Back-up Medication
(Per-Protocol Analysis)
Treated Episodes

Category	Placebo (N=96)		Antacid (N=99)		FAM 5 mg (N=97)		FAM 10 mg (N=94)		FAM 20 mg (N=105)	
	n	(Cum %)	n	(Cum %)	n	(Cum %)	n	(Cum %)	n	(Cum %)
No Backup	13	(14%)	16	(16%)	13	(13%)	15	(16%)	23	(22%)
0 to 1/3	23	(38%)	39	(56%)	38	(53%)	50	(69%)	43	(63%)
1/3 to 2/3	35	(74%)	30	(86%)	33	(87%)	20	(90%)	25	(87%)
2/3 to All	21	(96%)	13	(99%)	10	(97%)	8	(99%)	13	(99%)
All Backup	4	(100%)	1	(100%)	3	(100%)	1	(100%)	1	(100%)

Treatment Effect	Odds-Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	2.20	1.30, 3.72	8.56	0.0034
Placebo vs. 5 mg	1.99	1.17, 3.38	6.47	0.0110
Placebo vs. 10 mg	3.26	1.90, 5.58	18.50	0.0001
Placebo vs. 20 mg	3.17	1.88, 5.38	18.49	0.0001
Antacid vs. 5 mg	0.90	0.54, 1.53	0.14	0.7073
Antacid vs. 10 mg	1.48	0.87, 2.52	2.12	0.1454
Antacid vs. 20 mg	1.44	0.86, 2.42	1.96	0.1613
5 mg vs. 10 mg	1.64	0.96, 2.79	3.30	0.0692
5 mg vs. 20 mg	1.60	0.95, 2.68	3.14	0.0764
10 mg vs. 20 mg	0.97	0.58, 1.64	0.01	0.9241

Adapted from electronic submission RefP017p.75

Medical Officer Comments: The famotidine and antacid treatment groups had a lower proportion of heartburn episodes requring back-up medication compared to the placebo group (famotidine 20 mg, p=0.001; famotidine 10mg, p=0.001; famotidine 5 mg, p=0.011; antacid, p=0.003). There was no difference among the famotidine treatment groups and antacid group. There was numerically more patients in the famotidine 20mg group who reported no use of back-up medication.

Proportion of Heartburn Episodes Requiring Re-Medication

Patients were permitted to take an additional dose of test medication if heartburn persisted 3 hours after the first dose (re-medication). Each patient's proportion of episodes requiring re-medication was calculated by dividing the number of episodes which required re-medication by the total number of episodes the patient treated.

Proportion of Heartburn Episodes Requiring Re-Medication
Medians and Ranges
Per-Protocol Analysis
Treated Episodes

Placebo (n=96)		Antacid (n=99)		FAM 5 mg (n=97)		FAM 10 mg (n=94)		FAM 20 mg (n=105)	
Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
0	0-1	0	0-0.31	0	0-0.62	0	0-0.54	0	0-0.60

Adapted from electronic submission RefP017p.76

Proportion of Heartburn Episodes Requiring No Re-Medication
Per-Protocol Analysis
Treated Episodes

Category	Placebo (N=96)		Antacid (N=99)		FAM 5 mg (N=97)		FAM 10 mg (N=94)		FAM 20 mg (N=105)	
	n	(Cum %)	n	(Cum %)	n	(Cum %)	n	(Cum %)	n	(Cum %)
No Remed	57	(59%)	65	(66%)	65	(67%)	71	(76%)	72	(69%)
0 to 5%	9	(69%)	11	(77%)	8	(75%)	8	(84%)	7	(75%)
5% to 10%	8	(77%)	7	(84%)	11	(87%)	7	(91%)	8	(83%)
10% and Up	22	(100%)	16	(100%)	13	(100%)	8	(100%)	18	(100%)

Treatment Effect	Odds-Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	1.35	0.75, 2.44	1.00	0.3169
Placebo vs. 5 mg	1.41	0.78, 2.56	1.30	0.2544
Placebo vs. 10 mg	2.51	1.32, 4.75	7.95	0.0048
Placebo vs. 20 mg	1.48	0.82, 2.65	1.70	0.1927
Antacid vs. 5 mg	1.05	0.57, 1.92	0.02	0.8845
Antacid vs. 10 mg	1.86	0.97, 3.56	3.47	0.0624
Antacid vs. 20 mg	1.09	0.60, 1.98	0.08	0.7716
5 mg vs. 10 mg	1.77	0.92, 3.42	2.94	0.0863
5 mg vs. 20 mg	1.04	0.57, 1.90	0.02	0.8877
10 mg vs. 20 mg	0.59	0.31, 1.12	2.60	0.1070

Adapted from electronic submission RefP017p. 79

Medical Officer Comments: Only the famotidine 10 mg group showed significantly more favorable results than placebo (p=0.0048). All treatment groups showed numerically more favorable results than placebo.

Time to relieve First Heartburn Episode of Double-Blind Phase

For the first episode of the double-blind period, patients recorded their response to therapy at ½ hour, 1 hour, 1-½ hours, 2 hours and 3 hours. This was analyzed using survival methods. "Relief" was defined as a successfully treated episode: a response of "completely relieved" after I or 2 doses of medication (re-medication) without the use of back-up medication.

Time to Relieve First Heartburn Episode of Double-Blind Phase
Per-Protocol Analysis

Treatment Effect	Hazard Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	1.51	1.04, 2.20	4.58	0.0323
Placebo vs. 5 mg	1.35	0.92, 1.98	2.30	0.1293
Placebo vs. 10 mg	1.58	1.08, 2.33	5.41	0.0200
Placebo vs. 20 mg	1.28	0.88, 1.87	1.64	0.1997
Antacid vs. 5 mg	0.89	0.62, 1.28	0.39	0.5324
Antacid vs. 10 mg	1.05	0.73, 1.50	0.07	0.7977
Antacid vs. 20 mg	0.85	0.60, 1.21	0.85	0.3569
5 mg vs. 10 mg	1.17	0.81, 1.70	0.72	0.3960
5 mg vs. 20 mg	0.95	0.66, 1.37	0.08	0.7808
10 mg vs. 20 mg	0.81	0.56, 1.16	1.33	0.2490

Adapted from electronic submission RefP017p.82

Medical Officer Comments: The results shown above demostrates that patients in the famotidine 10 mg and antacid group (for per protocol analysis) and famotidine 5 mg (for intent-to-treat analysis) reported a faster time to relief of their first episode of heartburn compared to the placebo group.

Subgroups Analysis

There was no evidence of a treatment-by-factor interaction (p>0.050) for age, gender, or race for this study.

Complete Relief Within 1 Hour of Dosing
By Age Group

Treatment Group	Gender	N	Total Episodes	Unadjusted Proportion of Episodes with Complete Relief Within 1 Hour
Famotidine 20 mg	65 or under	102	2398	0.365
	Over 65	11	266	0.482
Famotidine 10 mg	65 or under	103	2492	0.338
	Over 65	6	150	0.794
Famotidine 5 mg	65 or under	102	2393	0.328
	Over 65	8	219	0.358
Antacid	65 or under	104	2320	0.321
	Over 65	8	239	0.246
Placebo	65 or under	100	2295	0.267
	Over 65	8	239	0.318
N = Number of patients				

Adapted from electronic submission RefP017p.1715

Less than 10% of the population in each group were ≥ 65 years old, the number is too small to do meaningful analysis.

Complete Relief Within 1 Hour of Dosing
By Race

Treatment Group	Race	N	Total Episodes	Model-Adjusted Probability of Complete Relief Within 1 Hour
Famotidine 20 mg	Caucasian	100	2390	0.400
	Non-Caucasian	13	274	0.220
Famotidine 10 mg	Caucasian	101	2452	0.339
	Non-Caucasian	8	190	0.399
Famotidine 5 mg	Caucasian	98	2296	0.320
	Non-Caucasian	12	316	0.192
Antacid	Caucasian	99	2306	0.315
	Non-Caucasian	13	253	0.149
Placebo	Caucasian	94	2195	0.244
	Non-Caucasian	14	339	0.169
N = Number of patients				

Adapted from electronic submission RefP017p.1717

There was no evidence of a treatment-by-factor interaction ($p>0.050$) for race (Caucasian vs. non- Caucasian) for this study.

Safety

For safety assessment, see Division of OTC Medical Officer's Safety Review.

Summary Statistics

Summary Statistics
"Per-Protocol Analysis"

Parameters	Weeks	Placebo	FAM 5 mg	FAM 10 mg	FAM 20 mg	Antacid	Statistical Significance FAM 5 mg	FAM 10 mg	FAM 20 mg	Antacid
Global Evaluation										
Good or Excellent (CUM %)		60%	69%	74%	75%	69%	*	*	**	
Number of Heartburn Episodes										
Treated Episodes Per 14 Days	Full Study	11.03	11.17	11.39	10.95	11.16				
Proportion of Episodes Relieved										
Treated Episodes Median		0.43	0.61	0.71	0.70	0.63	*	***+	***@	*
Proportion of Episodes Requiring Backup Medication										
Treated Episodes Median		0.41	0.33	0.22	0.25	0.32	*	***#	***#	**
Proportion of Episodes Requiring Re-medication										
Treated Episodes Median		0	0	0	0	0		**+		
Time to Relief of First Episode								*		*

* p<0.05 vs. placebo
** p<0.01 vs. placebo
*** p<0.001 vs. placebo

@ p<0.05 vs. FAM 5 mg and antacid
+ 0.05<p<0.10 vs. FAM 5 mg and antacid
# 0.05<p<0.10 vs. FAM 5 mg

Adapted from electronic submission RefP017p.111

Discussion

Medical Officer Comments: Protocol 017 is a double-blind, dose ranging study evaluating the effects of famotidine 5 mg, 10 mg, 20 mg, and antacid compared to placebo in the treatment of intermittent heartburn, taken as needed up to twice daily. Majority of the patients were Caucasians (89%) and the mean age was 44 years. Most patients had daily heartburn and there were slightly more males than females (54 vs. 46 %).

In this study, famotidine 20 mg was superior to placebo when patients globally assessed their response to treatment in the intent-to-treat analysis, however, in the per protocol

analysis, all of the famotidine groups were superior to placebo and there was no differences among the doses.

With regard to the proportion of heartburn episodes relieved, famotidine 20mg was significantly superior to placebo, antacid and famotidine 5 mg. When proportion of heartburn episodes completely relieved within *1 hour* dosing was assessed, both famotidine 20 mg and 10 mg were superior to placebo. In addition, the famotidine 20 mg group appear to have a numerically greater probability of complete heartburn relief (0.379; and the model-adjusted odds-ratio indicate that patients in this group were 1.17 and 1.98 times more likely to report complete relief compared to those in the 10 mg and placebo groups.

Each of the famotidine and antacid groups required less back-up medication compared to placebo, with no difference among the famotidine groups. Approximately 80% of patients used back-up medication for at least one heartburn episode during the study. It appears that there was numerically more patients in the famotidine 20 mg group who reported no use of back-up medication.

When assessing the proportion of heartburn episodes requiring re-medication, famotidine 20 mg did not show significant superiority to placebo, only numerically more favorable results. In the analysis of heartburn treated episodes, there was no difference among the treatment groups.

There was no evidence of a treatment-by-factor interaction ($p>0.050$) for age, gender, or race for this study.

For details of safety assessment, please see the Agency's Division of Over-the-Counter Drugs Medical Officer's Review.

Appendix E

Protocol 019 (P019)

A Double-Blind, Dose Ranging Study to Evaluate the Effects of Famotidine 10 mg, 20 mg, or Antacid, as Compared to Placebo as Needed up to Twice Daily in the Treatment of Intermittent Heartburn

Clinical Phase III

Study Period: December, 1989 to January, 1991

Hypotheses and Objectives

Hypotheses

- Famotidine 10 mg and 20 mg prn would relieve heartburn better than placebo as demonstrated by faster and more frequent pain relief.
- A single antacid tablet would relieve heartburn more effectively than placebo as demonstrated by faster and more frequent pain relief.

Objectives

- To assess the efficacy of famotidine vs. placebo in relief of heartburn.
- To assess the efficacy of antacid vs. placebo in relief of heartburn.
- Primarily assess when heartburn recurs after successful treatment.

Study Design

This was a randomized, double-blind, multicenter, parallel, placebo-controlled, at-home, multiple-episode treatment of heartburn trial. This study was conducted using 23 sites and included the following treatment groups: famotidine 20 mg, famotidine 10 mg, antacid, and placebo.

Patients with a history of heartburn requiring self-medication with antacid 3 or more times a week participated in a 1-week, single-blind, at-home, baseline phase. When patients developed heartburn, they recorded the initial severity of the episode on a diary card using a 4-point scale (Mild, Moderate, Severe, Very Severe). At hourly intervals following dosing for treatment of heartburn, patients recorded their response to study medication (single-blind antacid) using a 4-point scale: Completely Relieved (gone); Better (noticeably improved); Unchanged (not much different); and Worse (more severe). Patients qualified for randomization into the double-blind phase if they reported at least 3 episodes of heartburn improved within 1 hour by self-medication with single-blind antacid.

Patients who qualified for entry into the double-blind phase were randomized to 1 of 4 treatment groups. Randomized patients received at-home diary cards to record episodes of heartburn for a total of 4 weeks. Patients initially received test medication for

14 days, i.e., 28 famotidine/famotidine placebo tablets and 28 antacid/antacid placebo tablets. A second diary card and test medication for an additional 14 days was dispensed on 14th day.

Prior to dosing for each episode of heartburn, patients recorded the initial severity of the episode on the diary card using the 4-point scale described above. At hourly intervals following dosing for treatment of heartburn, patients recorded whether their heartburn was Completely Relieved, Better, Unchanged, or Worse, as compared to the severity of heartburn at the time of dosing. Patients assessed each dose of test medication hourly for 5 hours. Patients were also given rescue medication (open-label antacid) to use if the test medication was ineffective, the test medication was exhausted, or if heartburn occurred and both doses of test medication for that day were taken.

Clinical and Laboratory Measurements

	Baseline Phase	Double-Blind Phase		
	Visit 1	Day 1	Day 14	Day 28
1. Clinical				
History	X			
Complete Physical Exam	X			X
Interval History		X	X	X
Interval Physical Exam		X	X	
Adverse Reactions		X	X	X
Medication Counted		X	X	X
Diary Reviewed	X	X	X	X
Patient's Global Assessment				X
2. Laboratory				
A. Hematology				
Hemoglobin		X		X
Hematocrit		X		X
WBC		X		X
Differential		X		X
Platelet Count		X		X
B. Chemistry				
ALT (SGPT)		X		X
AST (SGOT)		X		X
Alkaline Phosphatase		X		X
Total Bilirubin		X		X
Creatinine		X		X
BUN		X		X

Adapted from electronic submission RefP019p.24

Concomitant Medications

- Concurrent therapy with any H_2-receptor antagonists, sucralfate, misoprostol or omeprazole was not allowed.
- Chronically administered medications for the treatment of secondary illnesses was allowed.
- Any medications taken by the patient were recorded on the case report form.
- No specific diet was prescribed during the study.

Study Population

Inclusion Criteria

- Males or females, age of 18 years or legal age of consent.
- Females of child-bearing potential had to be using, planned to continue using, a reliable means of contraception.
- A history of heartburn which required self-medication with antacid 3 or more times a week.
- Willing to participate in the study and undergo endoscopy twice and esophageal motility recording once and possibly twice.
- Willing to and able to complete a symptom diary.

Exclusion Criteria

- Less than 18 years old.
- Medically significant concurrent disease.
- Pregnant, lactating or of childbearing potential who were not using a reliable means of contraception.
- Inability to comply with the protocol due to concomitant psychiatric or medical condition.
- Presently with or within the preceding one month of enrollment, unstable heart disease.
- Any contraindication to upper gastrointestinal endoscopy or upper gastrointestinal motility study.
- Treatment of investigational drugs within one month prior to the study.
- Any other conditions which would have precluded the patient's participation in the study, in the investigator's opinion.
- Patients expected to require other H_2-receptor antagonists, sucralfate, misoprostol or omeprazole.

Evaluation Criteria

Efficacy

- Response to therapy: response to test medication was recorded up to 5 hours postdose. Patients used a therapy response scale to complete the statement, "*Compared to when I took the test medication, my heartburn is: Completely Relieved, Better, Unchanged* or *Worse.*" Patients also recorded on the Diary Card whether they required back-up medication, the *time* and *total* number taken. The number of heartburn experienced was also recorded.
- Global Assessment: at the conclusion of the study, patients rated their overall response to the test medication (excellent, good, fair, poor, none)

Statistical Planning Analysis

The data was analyzed to determine if the treatment groups differ with respect to the:

- number of episodes requiring self-medication occurring during the 4-week study
- patients global evaluation of the test drug upon completion of the study
- time onset of heartburn relief (looking specifically at a patient's first episode)
- proportion of episodes completely relieved of heartburn symptoms
- proportion of episodes requiring antacid rescue medication
- proportion of episodes requiring remedication

Logistic regression on global evaluation, proportion of episodes relieved, proportion of episodes requiring rescue medication, and proportion of episodes requiring remedication using SAS, PROC LOGISTIC. The model included terms for treatment, investigator, baseline episode severity, and baseline number of episodes. Likelihood test based on Poisson distribution for number of heartburn episodes. Survival analysis on time to relief of first episode using SAS, PROC PHGLM. The model included terms for treatment, investigator, and initial episode severity. A sample size of n=85 patients per group has 80% power to detect a 25% difference in proportion of episodes relieved between placebo and active treatment (at α=0.05, two tailed).

In the "per protocol analysis", patients were excluded if (1) concomitant H2-receptor antagonists were taken during the double blind phase of the study, (2) less than 3 heartburn episodes responsive to treatment within 1 hour, (3) lost efficacy data for the entire double blind phase. The following patients were considered evaluable: a total of 458 patients (placebo=113, antacid=116, famotidine 10 mg=114, famotidine 20 mg=115).

Ethics

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Results

Patient Characteristics

Baseline Patient Characteristics by Treatment Group
All Randomized Patients (N=509)

	Famotidine 20 mg (n=130)	Famotidine 10 mg (n=125)	Antacid (n=126)	Placebo (n=128)	Total (n=509)
Age (years)					
Mean	46.1	46.2	44.7	46.9	46.0
SD	14.8	14.6	13.7	15.6	14.7
Median	44.0	44.0	45.0	46.5	45.0
Range	20 to 80	20 to 79	20 to 75	18 to 83	18 to 83
N	130	125	126	128	509
Gender					
Male	57 (43.8%)	59 (47.2%)	59 (46.8%)	66 (51.6%)	241 (47.3%)
Female	73 (56.2%)	66 (52.8%)	67 (53.2%)	62 (48.4%)	268 (52.7%)
Racial Origin					
Caucasian	111 (85.4%)	116 (92.8%)	112 (88.9%)	110 (85.9%)	449 (88.2%)
Black	17 (13.1%)	8 (6.4%)	11 (8.7%)	14 (10.9%)	50 (9.8%)
Hispanic	1 (0.8%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	3 (0.6%)
Asian	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	2 (0.4%)
Indian	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.2%)
Oriental	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.2%)
Persian	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.2%)
Spanish	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.2%)
Vietnamese	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Frequency of Heartburn					
Daily	93 (71.5%)	79 (63.2%)	90 (71.4%)	93 (72.7%)	355 (69.7%)
Weekly	37 (28.5%)	45 (36.0%)	36 (28.6%)	35 (27.3%)	153 (30.1%)
Less often than weekly	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Most Frequent Cause of Heartburn					
Type of food	91 (70.0%)	76 (60.8%)	93 (73.8%)	90 (70.3%)	350 (68.8%)
Emotional stress	29 (22.3%)	38 (30.4%)	20 (15.9%)	28 (21.9%)	115 (22.6%)
Overeating	7 (5.4%)	5 (4.0%)	5 (4.0%)	3 (2.3%)	20 (3.9%)
Other	3 (2.3%)	6 (4.8%)	8 (6.3%)	7 (5.5%)	24 (4.7%)

Adapted from electronic submission RefP019p.25

Medical Officer Comments: The majority of the patients were Caucasians (88%), and the mean age was 46 years with an age range of 18 to 83 years. There were slightly more females than males (53% vs. 47%) and the frequency of daily heartburn for these patients was 70%. Baseline features were generally well balanced across treatment groups.

Patient Accounting

Patient Accounting for All Randomized Patients (N=509)

	Famotidine 20 mg	Famotidine 10 mg	Antacid	Placebo	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Total randomized	130	125	126	128	509
Completed study	122 (93.8)	121 (96.8)	114 (90.5)	122 (95.3)	479 (94.1)
Discontinued study	8 (6.2)	4 (3.2)	12 (9.5)	6 (4.7)	30 (5.9)
Clinical adverse experience	2 (1.5)	1 (0.8)	0 (0.0)	1 (0.8)	4 (0.8)
Lost to follow-up	0 (0.0)	3 (2.4)	5 (4.0)	1 (0.8)	9 (1.8)
No therapeutic response	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)	2 (0.4)
Patient uncooperative	5 (3.8)	0 (0.0)	7 (5.6)	2 (1.6)	14 (2.8)
Treatment of new condition	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.2)

Adapted from electronic submission RefP019p27

Medical Officer Comments: A total of 749 patients were enrolled in the baseline phase of the study; of these, 240 patients discontinued prior to randomization, therefore, only 509 patients were entered into the double blind phase. Only 479 patients (94%) completed the study. The most frequent reason for discontinuation was inadequate baseline heartburn relief, followed by patient being uncooperative and lost to follow-up. The number of patients entered into the study by treatment group is shown on the table above.

Efficacy

All patients who took study medication, provided heartburn relief data for at least 1 heartburn episode, and provided that for the baseline covariates, were included in the efficacy analyses. The efficacy analyses presented in this report are based on 500 patients with a total of 9951 episodes.

Global Evaluation

At the end of the 28-day double blind treatment period, patients globally assessed their response to treatment (excellent, good, fair, poor, none).

Global Evaluations
Per-Protocol Analysis

	Placebo (N=111) n (Cum %)	Antacid (N=108) n (Cum %)	FAM 10 mg (N=111) n (Cum %)	FAM 20 mg (N=113) n (Cum %)
Excellent	19 (17%)	25 (23%)	24 (22%)	41 (36%)
Good	49 (61%)	57 (76%)	61 (77%)	49 (80%)
Fair	37 (95%)	22 (96%)	23 (97%)	17 (95%)
Poor	4 (98%)	3 (99%)	3 (100%)	5 (99%)
None	2 (100%)	1 (100%)	0 (100%)	1 (100%)

Treatment Effect	Odds-Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	1.70	1.02, 2.83	4.21	0.0403
Placebo vs. 10 mg	1.70	1.03, 2.82	4.29	0.0384
Placebo vs. 20 mg	2.86	1.71, 4.77	16.17	0.0001
Antacid vs. 10 mg	1.00	0.60, 1.66	0.00	0.9953
Antacid vs. 20 mg	1.68	1.01, 2.80	3.96	0.0466
10 mg vs. 20 mg	1.68	1.01, 2.78	4.01	0.0452

Adapted from electronic submission RefP017p. 48

2-sided p-Values for Comparisons of Global Assessment

	Per Protocol	ITT
Antacid vs. Placebo	0.0403	0.0769
Famotidine 10 mg vs. Placebo	0.0384	0.0415
Famotidine 20 mg vs. Placebo	0.0001	0.0001

Medical Officer Comments: The results shown above demonstrate that all active treatment groups reported significantly better assessment than the placebo group in the "per protocol analysis" (famotidine 20 mg, p=0.001; famotidine 10 mg, p=0.038; antacid, p=0.04). In addition, patients in the famotidine 20 mg group reported significantly more favorable results than the famotidine 10 mg and the antacid groups (p=0.045 and p=0.040 respectively). In the intent-to-treat analysis, famotidine 20 mg was consistenly superior to famotidine 10 mg.

Number of Heartburn Episodes

Patients were allowed to self-medicate as needed for heartburn, up to twice daily during the study. The number of heartburn episodes was analyzed to determine whether active treatment reduced the total number of heartburn episodes over the course of the double blind treatment period.

14-Day Episode Rates
Per-Protocol Analysis
Treated Episodes

Treatment Group	Weeks 1 and 2 Rate	Weeks 1 and 2 S.E.	Weeks 3 and 4 Rate	Weeks 3 and 4 S.E.	Full Study Rate	Full Study S.E.
Placebo	10.73	0.31	10.34	0.31	9.93	0.20
Antacid	10.40	0.31	9.80	0.30	9.64	0.20
Famotidine 10 mg	10.02	0.30	9.25	0.29	9.15	0.19
Famotidine 20 mg	10.13	0.30	9.53	0.30	9.32	0.20

Treatment Effect	Weeks 1 and 2 Chi-Square	Weeks 1 and 2 p-Value	Weeks 3 and 4 Chi-Square	Weeks 3 and 4 p-Value	Full Study Chi-Square	Full Study p-Value
Placebo vs. Antacid	0.58	0.4458	1.54	0.2139	0.99	0.3203
Placebo vs. 10 mg	2.80	0.0940	6.66	0.0099	7.66	0.0056
Placebo vs. 20 mg	2.00	0.1575	3.62	0.0570	4.69	0.0304
Antacid vs. 10 mg	0.83	0.3632	1.75	0.1863	3.09	0.0790
Antacid vs. 20 mg	0.42	0.5194	0.43	0.5141	1.34	0.2476
10 mg vs. 20 mg	0.07	0.7865	0.45	0.5034	0.37	0.5442

Adapted from electronic submission RefP017p. 51

Medical Officer Comments: The data shows that both famotidine 20 mg and 10 mg appear to statistically reduce the number of heartburn episodes compared to placebo (p=0.03 and 0.005 respectively for full study results). This is more pronounced in the last 2 weeks of the double blind phase of the study.

Proportion of Heartburn Episodes Completely Relieved

Patients were allowed to self-medicate for heartburn as needed up to twice daily during the 4-week treatment study. Patients took one dose of "test medication" and then record their response; 1 hour later, if "complete relief" has not occurred, a "back-up medication" can be taken (an open-label antacid). Five hours later, if complete relief has not occurred, they were permitted to take a second dose of "test medication". To compare the treatment groups, the distribution of the categorized proportions of successfully treated episodes was analyzed.

Median Proportion of Heartburn Episodes Relieved
Per-Protocol Analysis
Treated Episodes

Placebo (n=113)	Antacid (n=112)	FAM 10 mg (n=112)	FAM 20 mg (n=115)
0.64	0.74	0.75	0.75

Adapted from electronic submission RefP017p.57

Median Proportion of Heartburn Episodes Relieved
Per-Protocol Analysis
Treated Episodes

Category	Placebo (N=113) n (Cum %)	Antacid (N=112) n (Cum %)	FAM 10 mg (N=112) n (Cum %)	FAM 20 mg (N=115) n (Cum %)
All Relieved	18 (16%)	23 (21%)	23 (21%)	20 (17%)
2/3 to All	33 (45%)	41 (57%)	41 (57%)	42 (54%)
1/3 to 2/3	44 (84%)	36 (89%)	32 (86%)	36 (85%)
0 to 1/3	16 (98%)	10 (98%)	11 (96%)	15 (98%)
None Relieved	2 (100%)	2 (100%)	5 (100%)	2 (100%)

Treatment Effect	Odds-Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	1.56	0.96, 2.54	3.28	0.0701
Placebo vs. 10 mg	1.52	0.94, 2.47	2.91	0.0879
Placebo vs. 20 mg	1.26	0.78, 2.03	0.87	0.3513
Antacid vs. 10 mg	0.97	0.60, 1.58	0.01	0.9144
Antacid vs. 20 mg	0.80	0.50, 1.30	0.79	0.3727
10 mg vs. 20 mg	0.82	0.51, 1.33	0.62	0.4318

Adapted from electronic submission RefP017p. 59

Complete Relief Within 1 Hour of Dosing

Complete Relief Within 1 Hour of Dosing
Efficacy Population (N=500)

Treatment Group	N	Total Heartburn Episodes	Model-Adjusted Probability of Complete Relief Within 1 Hour
Famotidine 20 mg	129	2512	0.362
Famotidine 10 mg	122	2364	0.325
Antacid	121	2456	0.301
Placebo	128	2619	0.217

N = Number of patients.

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
Famotidine 20 mg versus placebo	2.05 (1.48, 2.85)	18.36	<0.001
Famotidine 10 mg versus placebo	1.73 (1.26, 2.38)	11.58	<0.001
Famotidine 20 mg versus famotidine 10 mg	1.18 (0.85, 1.65)	0.97	0.325

Adapted from electronic submission RefP019p.31,Ref.2

Medical Officer Comments: This analysis shows that there was no significant difference among the treatment groups with regard to the proportion of heartburn episodes relieved, which is in contrast to the results of Study P017. However, with regard to the proportion relieved within 1-hour dosing, famotidine 20 mg and 10 mg were significantly superior to placebo (p<0.001). This latter result is similar to the findings in Study P017.

Proportion of Episodes Requiring Back-Up Medication

Patients took back-up medication (an open-label antacid) if heartburn persisted 1-hour after a dose of test medication. Each patient's proportion of heartburn episodes back-up medication was calculated by dividing the number of heartburn episodes which required back-up medication by the total number of episodes the patient treated during th study.

Median Proportion of Episodes Requiring Back-Up Medication
Per-Protocol Analysis
Treated Episodes

Placebo (n=113)	Antacid (n=112)	FAM 10 mg (n=112)	FAM 20 mg (n=115)
0.35	0.22	0.23	0.23

Adapted from electronic submission RefP017p. 64

Median Proportion of Episodes Requiring Back-Up Medication
Per-Protocol Analysis
Treated Episodes

	Placebo (N=113)		Antacid (N=112)		FAM 10 mg (N=112)		FAM 20 mg (N=115)	
Category	n	(Cum %)	n	(Cum %)	n	(Cum %)	n	(Cum %)
No Backup	20	(18%)	27	(24%)	28	(25%)	24	(21%)
0 to 1/3	36	(50%)	47	(66%)	45	(65%)	49	(63%)
1/3 to 2/3	40	(85%)	28	(91%)	26	(88%)	29	(89%)
2/3 to All	16	(99%)	9	(99%)	10	(97%)	11	(98%)
All Backup	1	(100%)	1	(100%)	3	(100%)	2	(100%)

Treatment Effect	Odds-Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	1.88	1.16, 3.07	6.45	0.0111
Placebo vs. 10 mg	1.88	1.15, 3.05	6.40	0.0114
Placebo vs. 20 mg	1.50	0.92, 2.43	2.69	0.1008
Antacid vs. 10 mg	1.00	0.61, 1.62	0.00	0.9892
Antacid vs. 20 mg	0.80	0.49, 1.29	0.85	0.3567
10 mg vs. 20 mg	0.80	0.49, 1.30	0.83	0.3624

Adapted from electronic submission RefP017p. 66

Medical Officer Comments: The famotidine 10 mg and the antacid groups reported significantly lower proportion of heartburn episodes requiring back-up medication. Famotidine 20 mg did not show any superiority (not even numerically) to placebo.

Proportion of Episodes Requiring Re-Medication

Patients were permitted to take an additional dose of test medication if heartburn persisted 5 hours after the first dose (re-medication). Each patient's proportion of episodes requiring re-medication was calculated by dividing the number of episodes that required re-medication by the total number of episodes the patient treated.

Proportion of Episodes Requiring No Re-Medication
Medians and Ranges
Treated Episodes

Placebo (n=113)		Antacid (n=112)		FAM 10 mg (n=112)		FAM 20 mg (n=115)	
Median	Range	Median	Range	Median	Range	Median	Range
0	0-0.53	0	0-0.46	0	0-0.65	0	0-0.75

Adapted from electronic submission RefP017p. 67

Proportion of Episodes Requiring Re-Medication
Medians and Ranges
Treated Episodes

	Placebo (N=113)	Antacid (N=112)	FAM 10 mg (N=112)	FAM 20 mg (N=115)
Category	n (Cum %)	n (Cum %)	n (Cum %)	n (Cum %)
No Remed	88 (78%)	87 (78%)	93 (83%)	96 (83%)
0 to 5%	6 (83%)	11 (88%)	4 (87%)	2 (85%)
5% to 10%	14 (96%)	6 (93%)	7 (93%)	4 (89%)
10% and Up	5 (100%)	8 (100%)	8 (100%)	13 (100%)

Treatment Effect	Odds-Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	1.08	0.56, 2.09	0.05	0.8148
Placebo vs. 10 mg	1.48	0.74, 2.93	1.24	0.2650
Placebo vs. 20 mg	1.45	0.73, 2.86	1.14	0.2858
Antacid vs. 10 mg	1.37	0.69, 2.71	0.79	0.3734
Antacid vs. 20 mg	1.34	0.68, 2.65	0.70	0.4038
10 mg vs. 20 mg	0.98	0.48, 1.99	0.00	0.9558

Adapted from electronic submission RefP017p.69

Medical Officer Comments: The famotidine 20 mg and 10 mg treatment groups showed numerically more favorable results in requiring no re-medication compared to placebo and antacid. However, none of the treatment comparisons was statistically significant.

Time to Relieve First Heartburn Episode of Double Blind Phase

For the first episode of the double-blind period, patients recorded their response to therapy at ¼ hour, ½ hour, 1 hour, 1-½ hours, 2 hours, 3 hours, 4 hours and 5 hours. This was analyzed using survival methods. "Relief" was defined as a successfully treated episode: a response of "completely relieved" after 1 or 2 doses of medication (re-medication) without the use of back-up medication.

Time to Relieve First Heartburn Episode of Double Blind Phase
Per-Protocol Analysis

Treatment Effect	Hazard Ratio	95% C.I.	Chi-Square	p-Value
Placebo vs. Antacid	0.95	0.69, 1.30	0.12	0.7308
Placebo vs. 10 mg	1.06	0.78, 1.46	0.14	0.7041
Placebo vs. 20 mg	1.24	0.90, 1.70	1.75	0.1857
Antacid vs. 10 mg	1.12	0.82, 1.54	0.53	0.4666
Antacid vs. 20 mg	1.31	0.96, 1.79	2.82	0.0931
10 mg vs. 20 mg	1.16	0.85, 1.59	0.91	0.3394

Adapted from electronic submission RefP017p. 72

Medical Officer Comments: This analysis demonstrated that none of the treatment comparisons was statistically significant. The results show that there is no benefit of famotidine over placebo in shortening the time to relieve the first episode of heartburn.

Subgroup Analysis

There was no evidence of a treatment-by-factor interaction (p>0.050) for age, gender, or race for this study. See tables below.

Complete Relief Within 1 Hour of Dosing
By Age Group

Treatment Group	Gender	N	Total Episodes	Unadjusted Proportion of Episodes With Complete Relief Within 1 Hour
Famotidine 20 mg	65 or under	108	2080	0.400
	Over 65	21	432	0.309
Famotidine 10 mg	65 or under	103	1927	0.388
	Over 65	19	437	0.178
Antacid	65 or under	108	2165	0.325
	Over 65	13	291	0.351
Placebo	65 or under	107	2081	0.251
	Over 65	21	538	0.216
N = Number of patients				

Adapted from electronic submission RefP019p1719

Complete Relief Within 1 Hour of Dosing
By Race

Treatment Group	Race	N	Total Episodes	Model-Adjusted Probability of Complete Relief Within 1 Hour
Famotidine 20 mg	Caucasian	110	2186	0.356
	Non-Caucasian	19	326	0.402
Famotidine 10 mg	Caucasian	113	2186	0.325
	Non-Caucasian	9	178	0.318
Antacid	Caucasian	108	2203	0.292
	Non-Caucasian	13	253	0.386
Placebo	Caucasian	110	2190	0.227
	Non-Caucasian	18	429	0.142
N = Number of patients				

Adapted from electronic submission RefP019p.1722

There was no evidence of a treatment-by-factor interaction ($p>0.050$) for race (Caucasian vs. non-Caucasian) for this study.

Safety
For safety evaluation, see Division of OTC Medical Officer's Safety Review.

Summary Statistics

Per-Protocol Analysis

Parameters	Weeks	Summary Statistics "Per-Protocol Analysis" Placebo	FAM 10 mg	FAM 20 mg	Antacid	Statistical Significance FAM 10 mg	FAM 20 mg	Antacid
Global Evaluation								
Good or Excellent (CUM %)		61%	77%	80%	76%	*	***	*
Number of Heartburn Episodes								
Treated Episodes Per 14 Days	Full Study	9.93	9.15	9.32	9.64	**	*	
Proportion of Episodes Relieved								
Treated Episodes Median		0.64	0.75	0.75	0.74	+		+
Proportion of Episodes Requiring Backup Medication								
Treated Episodes Median		0.35	0.23	0.23	0.22	*		*
Proportion of Episodes Requiring Re-medication								
Treated Episodes Median		0	0	0	0			

* p<0.05 vs. placebo
** p<0.01 vs. placebo
*** p<0.001 vs. placebo
+ 0.05<p<0.10 vs. placebo

Discussion

Protocol P019 is a dose ranging study evaluating the effects of famotidine 10 mg, 20 mg, and antacid when compared to placebo as needed, up to twice daily in the treatment of intermittent heartburn. Patients who participated in the study were mostly Caucasians, middle-aged, with slightly more females than males (53% vs. 47%). The frequency of daily heartburn for these patients was 70%.

In this study, for global assesssment of patients response to treatment, famotidine 20 mg was consistently superior to placebo and famotidine 10 mg. Both famotidine groups also appear to statistically reduce the number of heartburn episodes compared to placebo.

There was no significant difference among the treatment groups with regard to the proportion of heartburn episodes relieved, which is in contrast to the results of Study P017. However, with regard to the proportion relieved within 1-hour dosing, famotidine 20 mg and 10 mg were significantly superior to placebo ($p<0.001$). This latter result is similar to the findings in Study P017.

With regard to the proportion of episodes requiring back-up medication and time to relief of first heartburn episode, famotidine 20 mg did not show superiority over the other treatment groups. There was a numerical trend favoring both famotidine treatment groups in the proportion of patients requiring no re-medication compared to antacid and placebo.

There was no evidence of a treatment-by-factor interaction ($p>0.050$) for age, gender, or race for this study.

For details of safety assessment, please see the Agency's Division of Over-the-Counter Drugs Medical Officer's Review.

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/s/

Lolita Lopez
9/3/03 01:54:41 PM
MEDICAL OFFICER

Ruyi He
9/3/03 02:43:07 PM
MEDICAL OFFICER
This is the second part of efficacy review for
NDA 20325/SE2/015 which includes individual study reviews (appendices).

Joyce Korvick
9/3/03 03:24:08 PM
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