METHOD FOR PREVENTING HEARTBURN

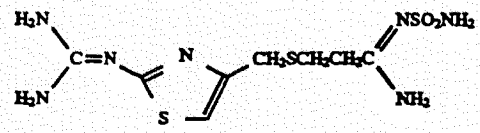
BACKGROUND OF THE INVENTION

Heartburn, or pyrosis, is a sensation of pain or burning located substernally or high in the epigastrium with radiation into the neck and occasionally to the arms, associated with regurgitation of acid-peptic gastric juice into the esophagus. Occasional heartburn is common in normal persons, but frequent and severe heartburn is generally a manifestation of esophageal dysfunction. Heartburn may result from abnormal motor activity or distention of the esophagus reflux of acid or bile into the esophagus, or direct esophageal mucosa irritation (esophagitis).

Heartburn is most often associated with gastroesophageal reflux. In this setting, heartburn typically occurs after a meal, with stooping or bending, or when the patient is supine. It may be accompanied by the spontaneous appearance in the mouth of fluid which may be salty, sour, or bitter and green or yellow. Heartburn may arise following the ingestion of certain foods (e.g. citrus fruit juices) or drugs (e.g. alcohol or aspirin).

Reflux esophagitis consists of esophageal mucosal damage resulting from reflux of gastric or intestinal contents into the esophagus. Esophagitis, an inflammation of the esophagus from regurgitation of acid gastric contents, producing substernal pain, develops when the mucosal defenses that normally counteract the effect of injurious agents on the esophageal mucosa succumb to the onslaught of the refluxed acid pepsin or bile. Mild esophagitis shows microscopic changes of mucosal infiltration with granulocytes or eosinophils, hyperplasia of basal cells, and elongation of dermal pegs. Erosive esophagitis shows endoscopically visible damage to the mucosa in the form of marked redness, friability, bleeding, superficial linear ulcers, and exudates.

Famotidine (available from Merck & Co., Inc., Whitehouse Station, N.J., under the name PEPCID®), an antagonist of the histamine H_2 receptor, is 3-{{{2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-N-(aminosulfonyl)propanimidamide, having the structural formula:



The primary clinically important pharmacologic activity of famotidine is inhibition of gastric secretion. Both acid concentration and volume of gastric secretion are reduced by famotidine. Famotidine is used to treat acid-related disorders such as gastric and duodenal ulcer, gastroesophageal reflux disease and Zollinger Ellison syndrome. Its safety and efficacy have been well established in controlled clinical studies. It is used by over 31 million patients worldwide.

Trials have shown famotidine to be beneficial in a dose dependent manner in relief of symptoms associated with ulcerations and gastritis.

Gitlin et al., *Amer. Journal of Gastroenterololg* (1985) vol. 80 pp. 840 examines famotidine efficacy in the treatment of active duodenal ulcers. The results suggest that duodenal ulcer healing rates are famotidine dosage dependent. 20 mg twice daily, 40 mg twice daily and 40 mg at bedtime were administered over a four week period. Healing rates of 67, 75, 70% , respectively, were seen.

Similarly, Miyoshi et al., *Naika Hokan* (1987) vol. 34 pp. 442–457 demonstrates that the efficacy of famotidine as a gastritis therapy is dose-related. Miyoshi et al. evaluated dosage regimens of 5, 10, or 20 mg twice daily in the treatment of gastritis symptom relief. Patients treated with 10 to 20 mg of famotidine had fewer erosions and mucosal haemorrhages than those treated with 5 mg famotidine.

McCallum et al., *Dig. Dis. Sci.* (1985) vol. 30 pp. 1139–1144 describes a study of healthy patients demonstrating that 5 mg of famotidine produces has an effect on gastric acid secretion. Laskin et al., *J. Clin. Pharmacol.* (1993) vol. 33 pp. 636–639 describes a study demonstrating that single doses of 5 and 10 mg of famotidine produces statistically significant decreases in intragastric acidity, beginning at 90–100 minutes and persisting for approximately 9 hours.

Applicants have now found that administration of famotidine, prior to consumption by patients of heartburn-inducing food or beverage, to patients who ordinarily experience heartburn episodes following consumption of such meals, is an effective means for preventing or minimizing symptoms associated with heartburn. Applicants have found that heartburn episodes can be prevented in patients ordinarily susceptible to heartburn episodes, if famotidine is administered in doses of between 5 mg and 20 mg, prior to ingestion of heartburn-inducing food and beverage. Applicants have also found that the risk of experiencing heartburn episodes can be reduced in patients ordinarily susceptible to heartburn episodes if such doses of famotidine are administered prior to ingestion of heartburn-inducing food and beverage. Applicants have also found that heartburn episodes in patients ordinarily susceptible to heartburn episodes can be relieved if such doses of famotidine are administered prior to ingestion of heartburn- inducing food and beverage.

Applicants have also found that the effectiveness of such treatment is not dose dependent.

SUMMARY OF THE INVENTION

The invention is a method for preventing heartburn episodes in a patient susceptible to suffering heartburn episodes following ingestion of heartburn-inducing food or beverage, comprising administering to the patient, prior to consumption by the patient of the food or beverage, a composition comprising an amount of famotidine between about 5 mg and 20 mg.

The invention is also a method for reducing the risk of heartburn episodes in a patient susceptible to suffering heartburn episodes following ingestion of heartburn-inducing food or beverage, comprising administering to the patient, prior to consumption by the patient of the food or beverage, a composition comprising an amount of famotidine between about 5 mg and 20 mg.

The invention is also a method for relieving heartburn episodes in a patient susceptible to suffering heartburn episodes following ingestion of heartburn-inducing food or beverage, comprising administering to the patient, prior to consumption by the patient of the food or beverage, a composition comprising an amount of famotidine between about 5 mg and 20 mg.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph representing heartburn severity in patients in response to administration to patients of famotidine 5 mg, famotidine 10 mg, famotidine 20 mg, or placebo, and subsequent ingestion by the patients of heartburn-inducing food or beverage.

FIG. 2 is a graph showing mean area under the curve scores for heartburn severity, acid sour stomach and overall discomfort.

assessment period or immediately prior to administration of rescue medication. Treatments were rated on a five-point scale as ineffective (0), poor (1), fair (2), good (3), or excellent (4). Efficacy was additionally assessed by examining the use of rescue medication and the time to rescue medication in each treatment group.

The tolerability of the four study treatments was determined by recording all adverse experiences reported by subjects during the trial.

Approximately equal numbers of males (58) and females (63) were studied, ranging in age from 20 to 61 years. Subjects had been experiencing meal-provoked gastrointestinal symptoms for approximately 7 years, having an average of 5.6 episodes per week. Ninety-seven subjects (80%) indicated that the validation meal produced symptoms similar to those provoked by a typical meal, and the severity of symptoms following the validation meal was rated as about the same or worse by 83% of subjects.

Global evaluations of study medication were significantly more favorable following all three doses of famotidine than following placebo for all four meals combined ($p<0.001$). More than half of all subjects receiving famotidine (54–63%) rated the drug as either "excellent"or "good" versus only 38% of subjects receiving placebo. The global evaluations of all treatments for the four test meals combined are shown in FIG. 3.

A peak heartburn rating was recorded for each participant. Each individuals' peak heartburn rating was ranked in a manner consistent with the symptom severity evaluation described above. Significantly milder peak heartburn ratings were evident following treatment with all three doses of famotidine compared to placebo ($p<0.001$ for famotidine 5 mg and famotidine 20 mg versus placebo; ($p=0.004$ for famotidine 10 mg versus placebo). Approximately three-quarters of famotidine subjects (74–76%) rated their peak heartburn severity as "mild", "slight", or "none". In contract, only 57% of subjects gave similar ratings following placebo treatment.

As shown in FIG. 1, mean heartburn severity tended to be equivalent in the placebo and famotidine dosage groups for the first hour, but for the remainder of time, it was greater in the placebo group than in the famotidine groups. Mean AUC scores (area under the curve) for heartburn across the 5 hour evaluation interval were significantly lower than in the famotidine 5-, 10-, and 20-mg dosage groups than in the placebo group (FIG. 2).

FIG. 2 also shows that mean AUC scores across the 5 hour assessment period for acid/sour stomach and overall discomfort were significantly smaller for each of the famotidine dosages than for placebo ($p\leqq0.025$ for acid/sour stomach; $p\leqq0.008$ for overall discomfort). In addition, peak rating of both acid/sour stomach and overall discomfort were also milder with famotidine prophylaxis than with placebo. Peak acid/sour stomach was rated as "mild", "slight", or "none" by 73%, 69%, and 68% of subjects following treatment with 5, 10, and 20 mg famotidine, respectively, and by 54% of subjects following placebo treatment. Similar percentages of subjects in the three famotidine dosage groups (77%, 66%, 74%) rated their peak overall discomfort as "mild" or less compared to only 54% of those treated with placebo. The comparison with placebo was statistically significant for all three dosages of famotidine for acid/sour stomach ($p<0.034$) and was statistically significant for the 5- and 20-mg dosages for overall discomfort ($p<0.001$).

A rescue antacid was used by only 17–18% of subjects in the three famotidine dosage groups compared to 37% of those treated with placebo ($p<0.001$). The differences between the famotidine and placebo groups were most evident 90 minutes following test meal ingestion.

With one exception, the differences between the three famotidine dosage groups were not statistically significant for any of the efficacy parameters ($p\geqq0.09$), nor was there evidence of a carryover effect of previous treatment ($p\geqq0.09$). The significant difference between the dosage groups was for overall discomfort where peak ratings following the 5- and 20-mg dosages were milder than those after 10 mg ($p\leqq0.019$).

A total of 61 subjects reported an adverse experience during the trial, with the incidence being approximately equal during each of the four treatment periods. No subject had a serious adverse experience during this trial, nor did any subject discontinue the study prematurely for safety reasons.

The results of the study show that administration of famotidine 1 h before a food and beverage challenge was significantly more effective than placebo in preventing provoked upper gastrointestinal symptoms. Peak ratings of heartburn and acid/sour stomach were significantly milder following administration of single oral doses of famotidine 5, 10, and 20 mg compared to placebo, and approximately three-quarters of subjects rated these symptoms as "none" to "mild" following prophylactic treatment with famotidine compared to slightly more than half following placebo. In addition, overall discomfort was rated as "mild" or less by a larger percentage of subjects following famotidine doses of 5, 10, and 20 mg (77%, 66%, and 74% respectively) than following placebo (54%). This difference was only statistically significant, however, for the 5- and 2-mg dosages. Global evaluations performed at the end of each test period also significantly favored famotidine over placebo, with 54–63% of subjects rating famotidine 5, 10, and 20 mg as "good" or "excellent" compared to only 38% of subjects for placebo. Consistent with these finding, rescue antacids were used by a significantly smaller percentage of subjects following famotidine treatment compared to placebo (17–18% versus 37%).

With the exception of peak overall discomfort ratings, there were no significant differences among the three famotidine dosages in this trial for any of the efficacy parameters evaluated, indicating that a dose as low as 5 mg was as effective as higher doses of 10 and 20mg.

Famotidine was well tolerated in this trial, with the type and frequency of reported adverse experiences similar to those observed with placebo. There was no distinction in the tolerability profile among the three famotidine dosages, confirming the notable absence of any dose-related change in the incidence of side effects reported in other investigational trials.

In summary, single oral doses of 5, 10, and 20 mg famotidine were significantly more effective than placebo in preventing food- beverage-induced heartburn and related upper gastrointestinal symptoms when given 1 hour before a provocative meal challenge. The tolerability of three dosages of famotidine was comparable to that of placebo.

What is claimed is:

1. A method for preventing heartburn episodes in a patient susceptible to suffering heartburn episodes following ingestion of heartburn-inducing food or beverage, comprising administering to the patient, 30 minutes prior to consumption by the patient of the food or beverage, a composition comprising an amount of famotidine of 10 mg.

* * * * *

Johnson & Johnson MERCK

CONSUMER PHARMACEUTICALS CO.

ORIGINAL

September 30, 1997

Lilia Talarico, MD, Director
Division of Gastrointestinal & Coagulation
Drug Products, HFD-180, Room 6B-45
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL NEW DRUG APPLICATION
NDA 20-902 FAMOTIDINE GELCAPS 10 MG

USER FEE ID No. [redacted]

Dear Dr. Talarico:

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, we are submitting a New Drug Application for Famotidine Gelcaps 10 mg. Johnson & Johnson o Merck Consumer Pharmaceuticals Co. is submitting this New Drug Application on behalf of Merck & Co. JJMCP will be responsible for all communications between the Food and Drug Administration and Merck Research Laboratories regarding NDA 20-902.

Pepcid AC Gelcaps is expected to be an effective alternate dosage form for the approved indications because it has been demonstrated to be bioequivalent to famotidine (Pepcid AC) 10 mg film-coated tablets (NDA 20-325, approved April 28, 1995).

This application is formatted as required in 21CFR 314.50 of the Code of Federal Regulations. It consists of a complete archival copy (blue binders), and five review copies in the appropriate colored binders as described in the attached Statement of Organization.

In accordance with the Prescription Drug User Fee Act of 1992, a check [redacted] in the amount of [redacted] was sent to the Food and Drug Administration, PO Box 3606909, Pittsburgh, PA on September 24, 1997.

Pursuant to 21CFR314(h)(3) a complete field copy of the Chemistry, Manufacturing and Controls technical section (Item 3) has been submitted to the FDA Philadelphia District Office. This field copy is a true copy of Item 3 as contained in the archival copy and review copies of this application.

Johnson & Johnson o Merck Consumer Pharmaceuticals Co. affirms that all sites listed in this application to support the manufacturing, packaging, and labeling of famotidine 10 mg gelcaps for the market are available for pre-approval inspection at the time of submission.

As required by 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we certify that, in connection with the application, the services of any person debarred under subsections 306(a) or (b) of the act were not and will not be used.

We consider the filing of this New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its existence public without first obtaining written permission.

If there are any questions concerning this application, please call me at (215) 233-7152 or in my absence, Edwin L. Hemwall, PhD (610) 397-2306.

Sincerely,

George Latyszonek

mhg
Attachment

EXCLUSIVITY SUMMARY FOR NDA # 20-902

Trade Name: Pepcid AC® Generic Name: famotidine

Applicant Name: Johnson & Johnson•Merck HFD #: 180

Approval Date If Known August 5, 1999

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES /_X_/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.):_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /___/ NO /_X_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

This application is approved based on demonstration of bioequivalence to the approved tablet formulation.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

-N/A -

Form OGD-011347 Revised 10/13/98

cc: Original NDA 20-902 HFD-180/Division File HFD-180/M.Folkendt HFD-93/Mary Ann Holovac

d) Did the applicant request exclusivity? YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? ____**NO**_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-325 nonprescription Pepcid AC (famotidine) Tablets
NDA # 20-801 nonprescription Pepcid AC (famotidine) Chewable Tablets
NDA #s 19-462, 19-510, 19-527, 20-249, 20-752 Pepcid (famotidine) Tablets, Injection, for Oral Suspension, Injection Premixed, and Orally Disintegrated Tablets.

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____
_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____
_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____