

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020801

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

John Hendt

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-801
Famotidine: Chewable Tablets, 10 mg
PEPCID Chewables™
Sponsor: Merck and Co., Inc. DEC 15 1997
Submission Date: December 18, 1996
Subject: DSI Recommendation for Reanalysis of Bioequivalence Data
Reviewer: Carol Cronenberger, Ph.D.



Synopsis

Famotidine 10 mg tablets (FCT) are currently available as an over-the-counter product in the US. The firm is currently seeking approval for the nonprescription use of famotidine coated-chewable tablets (CCT) as an alternative to the FCTs. The CCT may be of particular benefit to subjects who have difficulty swallowing.

The Office of Clinical Pharmacology and Biopharmaceutics completed its review of NDA 20-801 on Oct. 15, 1997 and found it to be acceptable based solely on Bioequivalence (BE) Study 089, which established BE between the and CCT.

Comments

The firm should reanalyze the data from BE Study 036 if they plan to use this information in any future submissions. Specifically:

- b. the data from Subjects #4, #10, and #14 should be excluded

Recommendations

The Division of Pharmaceutical Evaluation II recommends that the firm reanalyze the bioequivalence data from Study 036

Carol Cronenberger, Ph.D.
Division of Pharmaceutical Evaluation II

1/31

12/15/97

FT initialed by Lydia Kaus, Ph.D. /S/ 12/15/97
Team Leader, GI and Coagulation Drug Products

cc:NDA 20-801, HFD-180, HFD-870 (Chen), HFD-870 (Cronenberger), HFD-850
(Lesko), Central Document Room (Barbara Murphy).

J. Kenot

~~OCT 20 1997~~

Clinical Pharmacology and Biopharmaceutics Review

NDA 20-801

Submission Date: 12-18-96

PEPCID Chewables™

Famotidine Chewable Tablets: 10 mg

Sponsor: Merk and Co., Inc.
P.O. Box 4, BLA-20
West Point, PA 19486-0004

OCT 15 1997

Priority: 1S

Reviewer: Rajendra S. Pradhan, Ph.D.

Type of Submission: New Non-prescription Formulation

Synopsis:

For the nonprescription market, famotidine is currently available in the US as a 10 mg formulation. In order to provide patients with another option, a coated-chewable tablet (CCT) formulation has been developed by the sponsor. The CCT may be of particular benefit to patients who have difficulty swallowing tablets. In this application, the bioequivalence of 10 mg CCT formulation to the 10 mg formulation was evaluated (study 036). The mean dissolution of the CCT biobatch used in study 036 was [redacted]. This CCT formulation was then scaled up to a bigger batch. During the production scale up procedure the manufacturing equipment was changed and several CCT batches were manufactured. Some of these batches showed a slower in vitro dissolution profile. To investigate if these production scale batches differed in their in vivo performance, a second bioequivalence (BE) study (study 089) was conducted employing the batch that showed the slowest in vitro dissolution. The study 089 was considered to be the pivotal BE study for this NDA. Results of study 089 indicated that the slowest dissolution batch was also bioequivalent to the [redacted] formulation. The sponsor is requesting an approval of this new dosage form (CCT) based solely on this BE (089) study. In other words, the sponsor has not performed any clinical safety-efficacy trial for this new dosage form.

The dissolution measurements were conducted using 900 ml of medium using USP II apparatus with [redacted] and at 37 °C. The in vitro dissolution was conducted in 0.1 M phosphate buffer (pH 4.5). The sponsor is proposing an in vitro dissolution specification of [redacted].

Comments:

The sponsor makes the following statement in volume 1/page F-8 of this NDA:
 "During the recent testing of production scale-up, the manufacturing equipment was changed and a number of batches were prepared". This statement contradicts the statement made on volume 1/page F-18 which is as follows:
 "The tablets produced during scale-up were blended and compressed using the same scale of operation and the same equipment as that used for the original biobatch, yet these chewable tablets displayed a slower rate of dissolution at 30 minutes".

Recommendations:

The 10 mg CCT and 10 mg FCT are bioequivalent according to the two one-sided tests procedure and 90% confidence interval range of 80 to 125% using log-transformed data. The proposed in vitro dissolution specification is satisfactory. This submission is acceptable to the Div. of Pharmaceutical Evaluation II (DPE-II), OCPB.

/S/

10-10-97

Rajendra S. Pradhan, Ph.D.
Division of Pharmaceutical Evaluation II

APPEARS THIS WAY
ON ORIGINAL

FT initialed by Lydia Kaus, Ph.D. /S/ 10/15/97

cc: NDA 20-752, HFD-180, HFD-870 (MChen, Kaus, Pradhan), HFD-850 (Lesko), HFD-340 (Viswanathan), HFD-850 (Drug, Reviewer), Central Document Room (Barbara Murphy).

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020801

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 16, 1998

FROM: ^{Acting} Director,
^ Division of OTC Drug Products (HFD-560)

SUBJECT: Labeling Review
Pepcid AC (Famotidine) Chewable Tablets
NDA 20-801

TO: ~~Acting~~ Director,
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)

Attached is OTC's review of the draft labeling submitted by Merck Research Laboratories for the subject NDA.

/S/
Debra Bowen, M.D.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Pepcid AC NDA 20-801

Division of Over-the-Counter Drug Products
Labeling Review

NDA: 20-801
TYPE OF SUBMISSION: Amendment to a Pending Application.
Sponsor's Response to Approvable Letter
SPONSOR: Merck Research Laboratories.
DRUG PRODUCT: Pepcid AC Chewable Tablets
INDICATIONS: For relief of heartburn, acid
indigestion, and sour stomach.
For prevention of these symptoms
brought on by consuming food and
beverages
ACTIVE INGREDIENT: Famotidine 10 mg per tablet
SUBMISSION DATE: August 21, 1998
REVIEWER: Melvin Lessing
REVIEW DATE: September 4, 1998
PM: Al Rothschild

Background: Pepcid AC (famotidine) 10 mg tablets, manufactured by Merck Research Laboratories, is approved for OTC drug marketing for the relief of heartburn, acid indigestion and sour stomach, and also for the prevention of these symptoms brought on by consuming food and beverages. A New Drug Application (NDA 20-801) for a chewable tablet version of Pepcid AC was submitted on December 18, 1996, and approvable letters issued on December 19, 1997, and August 5, 1998. Responses to the approvable letter from Merck are dated February 5, 1998 and August 21, 1998, respectively. The August 21 response includes labeling for the 6, 18, 30, and 50 tablet cartons and a revised package insert.

A. The following changes were made in response to the August 5, 1998 approvable letter (see Attachment 1). The August 21, 1998 response includes labels for the 6, 18, 30, and 50 tablet cartons, and the package insert for the Pepcid AC Chewable Tablets.

1. The sponsor has revised the DIRECTIONS section on all
2. The sponsor has revised the storage statement on all
3. The sponsor has
4. The sponsor's suggested alternative allergy warning,

We are currently searching the FDA database for reports of cross-sensitivity of Pepcid with other acid reducers.

5. The 18 tablet carton label and the package insert are the same as the 18 tablet carton label and the package insert submitted on February 5, 1998, except for the added information described in numbers 1 and 2 above. The 6, 30, and 50 tablet carton labels are the same as the 18 tablet carton label, except for the statement regarding the number of tablets in the carton.

B. Recommendations:

1. The sponsor has revised portions of the label and committed to revise other portions of the label as requested in our approvable letters. The sponsor has also revised the package insert as requested in our approvable letters.
2. The sponsor's
at this time.
3. The sponsor
4. The labeling is acceptable.

In addition to the revisions specified above, we suggest that the labeling be revised, at the sponsor's earliest

convenience, so that it is in compliance with the February 27, 1997, Proposed Labeling Requirements for OTC Drug Products. For example, the labeling information headings

Please note that the Proposed Labeling Requirements for OTC Drug Products is subject to change pending publication of the final rule. Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

The sponsor should submit final printed labeling for all the packaging components, including the carton, dispenser, pouch, and the package insert.

/S/

Melvin Lessing P.D., (M/S)
Interdisciplinary Scientist, HFD-560

/S/

Helen Cothran, B.S.
Team Leader, HFD-560

APPEARS THIS WAY
ON ORIGINAL

/S/

Linda M. Katz., M.D., MPH
Deputy Director, HFD-560 9/16/98

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUL 10 1998
FROM: Director,
Division of OTC Drug Products (HFD-560)

SUBJECT: Labeling Review
Pepcid AC (Famotidine) Chewable Tablets -
NDA 20-801

APPEARS THIS WAY
ON ORIGINAL

TO: Acting Director,
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)

Attached is OTC's review of the draft labeling submitted by Merck Research Laboratories for the subject NDA.

/S/
Debra Bowen, M.D.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

**Division of Over-the-Counter Drug Products
Labeling Review**

NDA#: 20-801

TYPE OF SUBMISSION: Amendment to a Pending Application
Response to Approvable Letter

SPONSOR: Merck Research Laboratories

DRUG PRODUCT: Pepcid AC Acid Controller Chewable Tablets

INDICATION: For relief of heartburn, acid indigestion, and sour stomach. For prevention of these symptoms brought on by consuming food and beverages.

ACTIVE INGREDIENT: Famotidine 10 mg per tablet

SUBMISSION DATE: February 5, 1998

REVIEWER: Melvin Lessing

REVIEW DATE: June 8, 1998

PM: Al Rothschild

Background: Pepcid AC (famotidine) 10 mg tablets, manufactured by Merck Research Laboratories, is approved for OTC drug marketing for the relief of heartburn, acid indigestion and sour stomach, and also for the prevention of these symptoms brought on by consuming food and beverages. A New Drug Application (NDA 20-801) for a chewable tablet version of Pepcid AC was submitted on December 18, 1996, with an approvable letter being issued on December 19, 1997. The approvable letter requested specific information related to bioequivalence, chemistry, manufacturing and controls, and requested revisions to the submitted draft labeling. This review is of color mock-ups of the 18-tablet carton, the 30-tablet dispenser, the child-resistant sample pouch, the non-child resistant sample pouch, the single dose foil pouch, and the package insert.

Reviewer's Comments on the Proposed Revised Pepcid AC Chewable Tablet Labeling.

The following changes were made in response to the December 19, 1997 approvable letter (see Attachment 1). The sponsor's proposed labeling is in Attachment 2.

1. The sponsor has revised the Statement of Identity from "Acid Reducer/Famotidine 10 mg" to "Famotidine 10 mg/Acid Reducer" in

bold text throughout the text as requested in the approvable letter.

2. The sponsor has

3. The statement

4. The statement

5. The sponsor has revised

6. The sponsor has

7. Instructions concerning

8. The title

9. The sponsor has

10. The sponsor has chosen to delete the web site address in the labeling. The approvable letter stated that if the web site address is included in the labeling, all information on the web site must conform to approved labeling for the product.

11. The location of the expiration date and lot number has been identified on the 18 and 30 tablet cartons, as requested.

12. The sponsor acknowledged its obligation to remove the "NEW!" flag from all labeling within 6 months from date of introduction of the product.

Additionally, the sponsor has made the following changes:

1. On the left front panel and right front panel on the 30 count sample pouch dispenser, the statement

2. For reasons stated in comment 2 above, on the left front panel of the 30 count sample pouch dispenser, the section title

Agency Recommendations:

1. The application can be approved.

2. The sponsor should submit final printed labeling for all the packaging components, including the carton, dispenser, pouch, and the package insert.

The sponsor should be advised of the following modifications that should be incorporated in the labeling within 6 months, or at the next printing, whichever comes first.

1. The sponsor has bolded more information in the directions than FDA requested in the approvable letter. The approvable letter specified that only the following words/phrase in the directions

Pepcid AC NDA 20-801

be bolded: "**relieves,**" "**prevent,**" and "**60 minutes before.**"
Therefore, the directions for the carton, dispenser, pouch, and package insert must be revised to bold only the designated words.

2. The "**Uses**" section should be revised to denote "heartburn" as the primary symptom, with the other symptoms as secondary symptoms.

3. Under the "**Warnings**" section on the carton, dispenser, and

5. Concerning the issue

6. In the first and second bullets at the top of the back panel of the carton and dispenser, the sponsor needs to remove the

7. Note that since the December 19, 1997 approvable letter was

Pepcid AC NDA 20-801

issued, the text of bullet #3 under "Tips for Managing Heartburn" has been modified and simplified

8. On the back panel of the pouch, the warning (Tamper

In addition to the revisions specified above, we suggest that the labeling be revised, at the sponsor's earliest convenience, so that it is in compliance with the February 27, 1997, Proposed Labeling Requirements for OTC Drug Products. For example, the labeling information headings are presented with the first letter of the heading in upper case, followed by lower case letters and in the following specific order: **Active Ingredient(s), Purpose(s), Use(s), Warnings, Directions, Other Information, and Inactive Ingredients.** No other information should precede the "Active Ingredient(s)" section. (See prototype label in Attachment 3.) Please note that the Proposed Labeling Requirements for OTC Drug Products is subject to change pending publication of the final rule. Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

APPEARS THIS WAY
ON ORIGINAL

/S/

~~Melvin Lessing, R.D., M.S.~~
Interdisciplinary Scientist, HFD-560

/S/

~~Helen Cothran, B.S.~~
Team Leader, HFD-560

/S/

~~Rosemarie Neuner, M.D., MPH~~
Medical Officer, HFD-560

/S/

~~Linda M. Katz, M.D., MPH~~
Deputy Director, HFD-560 6/11/98

APPEARS THIS WAY
ON ORIGINAL

Attachments

NDA 20-801

Merck Research Laboratories
Attention: George Latyszzonek
Sunneytown Pike, BLA-20
West Point, PA 19486

DEC 19 1997

Dear Mr. Latyszzonek:

Please refer to your new drug application dated December 18, 1996, received December 19, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for nonprescription Pepcid[®] AC Acid Controller (famotidine) Chewable Tablets.

We acknowledge receipt of your submissions dated February 25; April 11; June 2; September 25; October 16 and 21; and November 10, 12, and 18, 1997. The User Fee goal date for this application is December 19, 1997.

We have completed the review of this application as submitted, with draft labeling submitted on November 11, 1997, and it is approvable. Before this application may be approved, however, it will be necessary for you to:

- A. Regarding the bioequivalence study #036, reanalyze the data with the following modifications to the data:
 - 1.
 2. Exclude data from subjects #4, #10, and #14.
- B. Regarding the Chemistry, Manufacturing and Controls (CMC) portion of the application:
 1. State the drug substance re-test period or expiry.
 2. Provide the established drug substance acceptance tests and specifications.
 3. Provide information regarding the drug product holding times, acceptance tests, and specifications for the following:
 - a. Transfer of the

- b. Transfer of the
- c. The bulk tablets prior to packaging.
4. Specify the holding time when transferring to the in the manufacturing process. In addition, provide a sampling plan for the
5. Provide the sampling plan used for in-process testing.
6. Provide the sampling plan used for release testing for conformity to the regulatory specifications.
7. Regarding provide the chemical structures, if known, and data relating
8. Explain the reason(s) for not including the method for in the regulatory specifications and methods.
9. Provide additional information regarding the detection by showing that the does not contain any other that may be formed
10. Regarding release testing, please state where this testing is performed.
11. Provide the sampling plan and acceptance testing for components of the container/closure system.
12. for the was reviewed and found The holder of this DMF has been notified of the
13. Be advised that the data submitted to date support an expiry period of 36 months, with a storage statement "Stored below 30°C (Protect from moisture)", only for the following two package types: PAPER and PET. However, the data submitted to date using foil strip pouches do not support the requested expiration date. Unless additional stability data are provided for the strip pouches to confirm the proposed expiry, a revised expiry period should be proposed for this proposed market presentation.

C. Regarding the labeling:

1. Revise the Statement of Identity from "Acid Reducer/Famotidine 10mg" to "Famotidine 10mg/Acid Reducer" in bold text throughout all the labeling to conform to 21 CFR 201.61.
2. The trade name for this drug product appears to be "Pepcid AC" rather than "Pepcid AC Acid Controller" in the proposed trade name graphic. Further, "Acid Controller" appears to be the statement of the general pharmacological category of the drug rather than "Acid Reducer". Revise the trade name graphic throughout all the labeling to the style approved in NDA 20-325 or propose a new trade name graphic that clearly identifies the trade name for this product as "Pepcid AC Acid Controller."
3. Add information on the phenylalanine content as required under 21 CFR 201.21(b) to all labels (immediate container foil wrap) and labeling (carton and package insert).
4. Move the statement "Do not use with other acid reducers" from the DIRECTIONS section to the WARNINGS section on all carton and pouch labeling.
5. Revise the DIRECTIONS statements on all labeling (carton, pouch, and package insert) to the following:
 - To relieve symptoms, chew 1 tablet thoroughly and swallow with a full glass of water.
 - To prevent symptoms, chew 1 tablet thoroughly and swallow with a full glass of water 60 minutes before eating a meal that you expect to cause symptoms.
6. Identify the location where the expiration date and lot number will be placed on the 16 and 30 tablet carton.
7. Instructions for using both the "swallowable tablet" and the "chewable tablet" formulations in the package insert is confusing to the consumer. Delete the instructions for using the "swallowable tablet" formulation from the package insert for this drug product.
8. Revise the directions statement in the "How to use PEPCID AC Acid Controller" section of the package insert from "...with water..." to "...with a full glass of water..."

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

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

If you have any questions, please contact Michael Folkendt, Project Manager, at (301) 443-0487.

Sincerely yours,

/S/

APPEARS THIS WAY
ON ORIGINAL

/S/

12-19-97

Debra Bowen, M.D.
Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Attachment 243

13 Page(s) Redacted

DRAFTING
LABELING

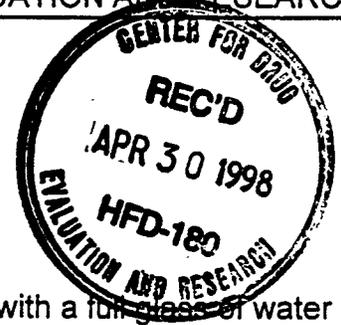
Mike

Jo Hendt

TO: NDA 20-801
CC: m. Folkendt, HFD-180

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 8, 1998
FROM: Rosemarie Neuner, MD, MPH, */S/*
Medical Officer
Division of OTC Drug Products, HFD-560



SUBJECT: Consumer directions re: swallowing medication with a full glass of water

TO: Ms. Helen Cothran, IDS
Team Leader
Div. Of OTC Drug Products, HFD-560

THROUGH: Linda M. Katz, MD, MPH */S/* 4/28/98
Deputy Dir., Div. Of OTC Drug Products, HFD-560

THROUGH: Debra L. Bowen, MD */S/* 4/25/98
Director, Div. Of OTC Drug Products, HFD-560

Merck Research Laboratories, the sponsor of Pepcid AC (famotidine) Acid Reducer Tablets (NDA 20-325), has submitted for agency review a supplemental NDA (S-007) for a change in time to take this product from 1 hour to 15 minutes prior to a meal for the prevention of heartburn. On review of this application the agency requested that the sponsor revise the "DIRECTIONS" section of the label to read "...swallow 1 tablet with a full glass of water." In response to the approvable letter dated December 23, 1997 requesting this labeling change, the sponsor has sent a letter dated February 27, 1998 in which they state that they have decided to keep the present directions as follows: "... swallow 1 tablet with water." The sponsor's reason for doing so is because the 2 pivotal studies (Protocols 092 and 093) submitted in support of this application were conducted using 3 ounces of water to swallow the study medication. The 2 bioequivalence studies (036 and 089) were done with 5 ounces and 4 ounces of water. All of the pivotal studies done for the marketed film-coated tablet formulation of this product were done with 3-4 ounces of water. Thus, there is no clinical data to support taking this product with a "full glass" of water. The sponsor also states that the word "full" fails to specify an actual volume of water, and does not help the consumers since the latter will be determined by the size of the glass used by the consumer.

I discussed this issue with Dr. E. Dennis Bashaw, Team Leader and reviewer for the FDA's Division of Biopharmaceutics. The general recommendation for tablets of any type is to be taken with a "full glass of water" which traditionally means 8 ounces of water. A volume of 8 ounces ensures that a sufficient volume of water is present in the stomach to facilitate dissolution of the drug as well as esophageal transit of the tablet.

The volume swallowed with a tablet becomes a nonissue when the drug is capable of dissolving in the amount of fluid administered so that bioavailability is not affected.

In the case of this product, Pepcid AC (famotidine) Acid Reducer Tablets, the sponsor's trials were conducted with 3-5 ounces of water being swallowed by the patients. Although more volume was used in the 2 bioequivalence trials done by the sponsor in support of this application, clinical efficacy was achieved using smaller amounts in the pivotal trials. Thus, there is no reason to request solubility data for this product from the sponsor at this time.

The amount of water used to take medication is a consumer safety issue. It is important for consumers to be aware that they need to take more than just a few sips of water as implied by the present directions which state "... take 1 tablet with water" to insure both proper esophageal transit and gastric dissolution of the ingested drug. In view of the vast array and variability in glassware size, modification of the directions to read "... swallow with a glass of water" would increase the likelihood that an adequate volume of fluid was ingested to insure appropriate transit and dissolution of the medication.

APPEARS THIS WAY
ON ORIGINAL

Final Recommendations:

Thus, it is the opinion of this medical officer that the labeling directions for all OTC H2 blockers be modified to state "...swallow with a glass of water."

- CC: OLE 6 NDA 20524
- HFD-560 Div. File
- HFD-560 Dir/Bowen
- HFD-560 Dep Dir/Katz
- HFD-560 MO/Neuner
- HFD-560 Team Leader/Cothran
- HFD-560 CSO/Rothschild
- HFD-560 IDS/Robinson
- HFD-560 IDS/Lessing
- HFD-880 Biopharm Team Leader/Bashaw

APPEARS THIS WAY
ON ORIGINAL

~~Handwritten signature~~
Falkenberg

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 18, 1997

FROM: Michael Folkendt
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Lilia Talarico, M.D. *15/12-18-97*
Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

TO: NDA 20-801
Pepcid AC Acid Controller (famotidine) Chewable Tablets, 10 mg

SUBJECT: Comments on 12/18/97 labeling review for NDA 20-801

This application provides for a new chewable tablet dosage form for nonprescription Pepcid AC Acid Controller (famotidine). The labeling review for this application was completed by the Division of Over-The-Counter Drug Products, HFD-560, on December 18, 1997 with recommendations for a number of revisions to the labeling. The following are comments on this labeling review and for an addition recommendation for a labeling revision:

1. Regarding the recommended revisions based the February 27, 1997 proposed rule published in the Federal Register (items 1 and 4), these revisions are, as stated in the cover memoranda for the labeling review by Dr. Debra Bowen, only advisory and are not required until the rule is final. Until the rule is finalized, any proposed labeling revisions based on this proposed rule are premature. However, the firm can be reminded of the proposed rule in the approvable letter with the following statement:

"If the February 27, 1997 Federal Register Notice "Over-The-Counter Human Drugs; Proposed Labeling Requirements" [62 FR 9023] becomes final before this application is approved, further revisions of the labeling format may be necessary.

2. Concerning the addition of the web site address on the labeling, because the reference to the web site is on the label it effectively incorporates the web site as part of the labeling. The regulations state that the label cannot be false and misleading in any particular. This web site includes the following claim for Pepcid AC Acid Controller:

"Nothing's worse than waking up in the middle of the night because of

heartburn. PEPCID AC has what it takes to control acid all night.* Just take one tiny PEPCID AC tablet before dinner and you can be heartburn-free the whole night long!”

After consulting with Bob Heller and Bob Eshelman of the Division of Drug Labeling and Nonprescription Drug Products, although the Agency does not have a policy on web sites at this time, they recommended the following wording be sent to the firm:

“Concerning the placement of the web site address on the labeling, we believe that this extends your labeling to the web site. Therefore, all information on this web site, such as “...heartburn-free the whole night long!”, must conform to the approved labeling for the drug product.”

3. The trade name for this drug product appears to be “Pepcid AC” rather than “Pepcid AC Acid Controller” in the proposed reformatted trade name graphic. Further, the text “Acid Controller” appears to be the statement of the general pharmacological category of the drug rather than “Acid Reducer”. The firm should be requested to revise the trade name graphic throughout the labeling to the style approved in NDA 20-325 or propose a new trade name graphic that clearly identifies the trade name for this product as “Pepcid AC Acid Controller.”

cc: Archival NDA 20-801
HFD-560/Division Files
HFD-180/M.Folkendt
HFD-180/L.Talarico
HFD-560/S.Walther
HFD-560/M.Lessing
HFD-560/D.Bowen
HFD-560/L.Katz

APPEARS THIS WAY
ON ORIGINAL

drafted by: mf/December 18, 1997
initialed by: L.Talarico 12/18/97
finaled: 12/18/97
filename: 20801712.MEM

MEMORADUM

HFD-180
J. Kendt

MEMORANDUM

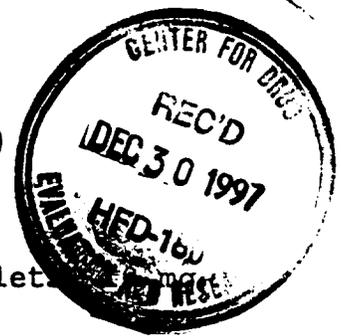
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 18, 1997

FROM: Director
Division of OTC Drug Products (HFD-560)
Office of Drug Evaluation V

SUBJECT: Labeling Review
Pepcid AC Acid Controller Chewable Tablets
NDA 20-801

TO: Director
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Office of Drug Evaluation III



Please find our labeling review attached. We have also included a prototype label using the new format proposed in the February 27, 1997 Proposed Labeling Requirements for OTC drugs.

We received your previous comments declining our recommendations for the new OTC labeling format prototype and for the suggested changes to the indications section of the label. As we discussed, these are recommendations and not requirements which we believe should be conveyed to the applicant.

APPEARS THIS WAY
ON ORIGINAL

/s/
Debra L. Bowen, M.D.

Attachments

Division of OTC Drug Products
Labeling Review

NDA#: 20-801

SPONSOR: Merck Research Laboratories

DRUG PRODUCT: Pepcid AC Acid Controller
Chewable Tablets

ACTIVE INGREDIENT: Famotidine 10 mg

DATE OF SUBMISSION: December 18, 1996

REVIEWER: Melvin Lessing, IDS

DATE OF REVIEW: November 28, 1997

CSO: Sakineh Walther

INDICATION: For relief of heartburn, acid indigestion, and sour
stomach

For prevention of these symptoms brought on by
consuming food and beverages

BACKGROUND: Merck Research Laboratories submitted an NDA on
December 18, 1996 to provide for a 10 mg chewable tablet dosage
form for famotidine for over-the-counter (OTC) use. On November
11, 1997, the sponsor submitted an amendment to the pending
December 18, 1996 NDA. The sponsor states that the November 11,
1997 amendment represents a reformatting of the front panel
graphics and provides distinguishing features for the chewable
tablets.

The amendment contains labeling for the 16 tablet carton
(Attachment 1), a package insert (Attachment 2), the 30 tablet
dispenser (Attachment 3), the child resistant sample pouch
(Attachment 4), the non-child resistant sample pouch (Attachment
5), and the single dose foil pouch (Attachment 6). The 6 tablet
carton is not included in this amendment, but was submitted with
the December 18, 1996 NDA.

REVIEWER'S COMMENT: This review is based on comparison of final
printed labeling of Pepcid AC Acid Controller Tablets dated July
10, 1995, and the February 27, 1997 Proposed Labeling
Requirements for OTC Drugs.

1. 16 Tablet Carton (Attachment 1)

1. Top Panel:

1a. The arrangement and repositioning of the components of the
trade name and statement of identity (SOI), including the text
"Pepcid AC Acid Controller," "Acid Reducer/Famotidine 10 mg."
and "Chewable" have been incorporated in the new graphic located

on the front and side panels.

REVIEWER'S COMMENT:

1a. To be consistent with the SOI printed on the principal display panel, the format of the SOI needs to be changed in accordance with 21 CFR 201.61. The SOI should also be bolded (See comment 2a below).

1b. The text "NEW! Reclosable Package" is new.

REVIEWER'S COMMENT:

1b. For this new chewable tablet dosage form, the word "NEW" should be used in the labeling no more than 6 months.

2. Front and Side Panels:

2a. The arrangement and repositioning of the components of the trade name and statement of identity, including the text "Pepcid AC Acid Controller," Acid Reducer/Famotidine 10 mg" and "Chewable" have been incorporated in the new graphic located on the front and side panels.

REVIEWER'S COMMENT:

2a. The SOI is not in the correct format according to 21 CFR 201.61. The established name of the drug should be followed by the pharmacologic category. Thus, the SOI should read:

Famotidine 10 mg/Acid Reducer

Additionally, the SOI should be in bold type.

2b. The text "NEW!" is larger and slanted.

REVIEWER'S COMMENT:

2b. Same comment as in 1b above.

3. Back Panel:

3a. The text "ACID REDUCER/FAMOTIDINE TABLETS 10 mg" was capitalized, but now only the first letter of each word is capitalized. The text is no longer bolded.

REVIEWER'S COMMENT:

3a. Same comment regarding the SOI as in 2a above.

3b. The following information is at the top of the back panel, above the active ingredient information.

REVIEWER'S COMMENT:

3b. It should be noted that in the February 27, 1997 Proposed Labeling Requirements for OTC Drugs and in the prototype labeling based on that proposal (see Attachment 7), no other information should precede the Active Ingredients section. The required information, i.e., Active Ingredients, Purpose, Use, Warnings, etc., shall be the information that appears on the product container or label.

3c. The active ingredient information "Famotidine 10 mg per chewable tablet" has been moved to above "Uses" instead of near the bottom of the package on the right-hand side.

REVIEWER'S COMMENTS:

3c. In accordance with the February 27, 1997 Proposed Labeling Requirements for OTC Drugs, the sponsor should add: The Purpose to the right of Active Ingredient as follows:

Active Ingredient (In Each Tablet)	Purpose
Famotidine 10 mg.....	Acid Reducer

3d. Under DIRECTIONS, the sponsor

REVIEWER'S COMMENTS:

3e. The sponsor has

REVIEWER'S COMMENT:

3e. In the new proposed labeling (see Attachment 7), "Do not use with other acid reducers" is a Warning, not a Direction.

3f. Under WARNINGS, the sponsor has included the following warning:

REVIEWER'S COMMENT:

3f. This warning is revised under the new proposed labeling format as a bulleted warning as follows:

3g. REVIEWER'S COMMENTS:

The location of the expiration date and lot number should be identified on the carton labeling.

4. Package Insert (Attachment 2)

Front Page

4a. The SOI reads

REVIEWER'S COMMENT:

4a. As discussed in 1a and 2a above, the SOI should read:

4a. In the section titled "How to use PEPCID AC Acid

Controller," the sponsor has added instructions and accompanying illustrations for using both the _____ and the chewable tablets.

REVIEWER'S COMMENT:

4a. In the section "How to use Pepcid AC Acid Controller," the sponsor has included instructions for using both the "tablet" _____ and the "chewable tablet." The instructions for the _____ tablet should be deleted. A package insert with instructions for two different products is confusing. Also, in this same section, the directions should be revised to direct consumers to swallow the chewable tablet with _____ " as stated in comment 3d above.

4b. In the section _____ has included _____

REVIEWER'S COMMENT:

4b. In this section we recommend that the language used in the prototype label in Attachment 7 "Tips for Managing Heartburn" be used.

Back Page

4c. Under the section "Proven effective in clinical studies," the sponsor has included graphs representing clinical studies for relief and prevention of heartburn.

REVIEWER'S COMMENT:

4c. The sponsor needs to remove the "x% better" headers located at the top of each graph because this information is promotional and confusing to consumers.

5. 30 Tablet Dispenser (Attachment 3)

5a. The labeling is similar to the 16 tablet labeling. The text "FOR PROFESSIONAL USE ONLY · NOT FOR RETAIL SALE," has been added to the top panel.

REVIEWER'S COMMENTS:

- 5a. We reiterate the comments as discussed above regarding the following items:
- (a) revise the SOI as discussed in comments 1a and 2a (applies to all front panels and the back panel)
 - (b) the use of "NEW" in comment 1b (applies to front panel)
 - (c) insert "full glass of water," and Warnings before Directions in comment 3d (applies to all front panels and back panel)
 - (d) labeling format in comment 3b (applies to back panel)
 - (e) addition of Purpose in comment 3c (applies to back panel)
 - (f) Warning format in comments 3e and 3f (applies to back panel)
 - (g) identify location of lot number and expiration date in comment 3g
 - (h) replace "How to help avoid symptoms" in comment 4b with "Tips for Managing Heartburn" (See Attachment 7) (applies to left front panel)
 - (i) revise headers on graphs in comment 4c (applies to right front panel)

6. Child Resistant Sample Pouch (Attachment 4)

The front panel of the pouch states that the unit contains "1 mint tablet." The front panel provides a dotted line for the consumer to cut open. The appearance and information are similar to the 16 tablet carton. The back also provides a dotted line to use in opening the pouch. The back also provides a warning "DO NOT USE IF POUCH IS OPEN OR BROKEN."

The back of the pouch contains the required phenylalanine statement, but other inactive ingredients are not listed.

REVIEWER'S COMMENTS:

6a. We have the same comments as in 1a, 1b, 2a, 3c, 3d, 3e, 3f, and 3g above.

7. Non-Child Resistant Sample Pouch (Attachment 5)

This pouch is the same as the Child Resistant Sample Pouch except that the back of the pouch includes the admonition: "FOR PROFESSIONAL USE ONLY · NOT FOR RETAIL SALE"

There is no dotted line on either side of the pouch or instructions on how to open the pouch.

REVIEWER'S COMMENTS:

7a. We have the same comments as for the Child Resistant Sample

Pouch above.

8. Single Dose Foil Pack (Attachment 6)

The front panel identifies the drug and its dose and indicates that the pouch contains one tablet. The back panel shows the distributor, lot number, and expiration date.

REVIEWER'S COMMENT:

8a. The minimum requirements for a single dose package are that the package contain the following: name/address of manufacturer, ingredient statement, lot number, and expiration date. In addition, as per 21 CFR 201.21, the labeling of all OTC products containing aspartame as an inactive ingredient must bear a statement informing phenylketonurics of the phenylalanine content. Therefore, the sponsor needs to add the phenylalanine content statement to the foil package.

RECOMMENDATIONS:

1. The word "NEW" should be used in the labeling for no more than six months.
2. It is suggested that the sponsor revise this labeling so that it is in compliance with the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products. A prototype label is attached. (See Attachment 7.) Note that as part of the acid reducer class consumer labeling, the "Uses" section is revised to denote heartburn as the primary symptom, with other symptoms being secondary. Refer to Attachment 7 for actual wording modification. Under the "Do Not Use" section, bulleted warnings have been added to not take this product if the consumer is allergic to acid reducers and also not to take the product with other acid reducers. The latter warning is included to avoid unintentional over-medicating by consumers. The labeling information is also presented in the following specific order: **Active Ingredient(s), Purpose(s), Use(s), Warnings, Directions, Other Information, and Inactive Ingredients.** Additional format and wording changes from the currently approved label are included.
3. The SOI printed on the principal display panel and elsewhere in the labeling is in the incorrect format. The format of the SOI needs to be changed in accordance with 21 CFR 201.61. The SOI should also be bolded. The SOI should contain the

established name of the drug followed by the pharmacologic category, and should read:

4. In accordance with the February 27, 1997 Proposed Labeling Requirements for OTC Drugs, the sponsor should add: The Purpose to the right of Active Ingredient as follows:
5. "Do not use with other acid reducers" should be under "Warnings," not "Directions."
6. The "Directions" should be revised
7. The location of the expiration date and lot number should be identified on the 16 tablet carton and the 30 tablet dispenser.
8. The sponsor's provision of a web site may be acceptable, more specific information will be necessary before making such a determination.
9. In the package insert, in the section "How to use Pepcid AC Acid Controller," the sponsor has included instructions for using both the "tablet" and the "chewable tablet." The instructions for the tablet should be deleted. A package insert with instructions for two different products is confusing. Also, in this same section, the directions should be revised to direct consumers to swallow the tablet with "a full glass of water."
10. In the package insert and 30 tablet dispenser, in the section "Excess acid: a burning problem," subsection "How to help avoid symptoms," please refer to the "Tips for Managing Heartburn" in the prototype label in Attachment 7. We recommend that the "Tips for Managing Heartburn" language be used in this section.
11. On the back page of the package insert and the 30 tablet dispenser, the sponsor needs to remove the "x% better" headers located at the top of each graph because this information is

promotional and confusing to consumers.

12. The phenylalanine content statement needs to be added to the single dose foil pack as required by 21 CFR 201.21.

13. The above recommendations, as appropriate, are also applicable to the 6 tablet carton.

/S/

~~Melvin Lessing, P.D., M.S.
Interdisciplinary Scientist, HFD-560~~

/S/

APPEARS THIS WAY
ON ORIGINAL

~~Helen Cothran, IDS
Team Leader, Team 4, HFD-560~~

/S/

~~Linda M. Katz, MD, MPH
Deputy Director, HFD-560~~

- cc: orig NDA
- HFD-560/Div. File
- HFD-180
- HFD-560 Lessing
- HFD-560 Cothran/Robinson/Neuener/Walther/Katz/Bowen

/S/ 12/18/97

APPEARS THIS WAY
ON ORIGINAL

29 Page(s) Redacted

DRAFTING LABELING

REQUEST FOR TRADEMARK REVIEW

Folkendt
980

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	HFD-180
Attention: Michael Folkendt /S/ 3/4/98	Phone: (301) 443-0487
Date: March 4, 1998	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Pepcid AC	NDA/ANDA# NDA 20-801
Established name, including dosage form: famotidine chewable tablets, 10 mg	
Other trademarks by the same firm for companion products: Please note that this product, as well as the swallowable tablet (NDA 20-325), is for the OTC market place. Higher strengths of this drug is also marketed R under the trade name "Pepcid".	
Indications for Use (may be a summary if proposed statement is lengthy): Treatment and prevention of heartburn.	
Initial Comments from the submitter (concerns, observations, etc.):	
1. Attached to this request is the submission containing the request (highlighted in yellow) to change the trade name of the drug from "Pepcid AC Acid Controller" to "Pepcid AC" and the resulting proposed labeling. I have also attached the original opinions received from your committee when this drug was under review to be marketed in the OTC market place.	
2. The Division of OTC Drug Product is currently evaluating this labeling as a whole.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-801; HFD-180/division file; HFD-180/M.Folkendt

Rev. December 95



CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 980

HFD# 180

PROPOSED PROPRIETARY NAME:

APPLICANT: MICHAEL FOLKENDT

PEPCID AC

A. Look-alike/Sound-alike

Potential for confusion:

Low Medium High

B. Misleading Aspects

C. Other Concerns

The sponsor wishes to remove "acid controller" from the labeling of this product. The Committee has no objection to this removal.

D. Established Name

Satisfactory

Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations: ACCEPTABLE UNACCEPTABLE

F. Signature of Chair/Date

ISI ; 4/13/98

EXCLUSIVITY SUMMARY for NDA # 20-801 SUPPL # -----
Trade Name Pepcid AC Generic Name famotidine
Applicant Name Johnson & Johnson-Merck HFD- 180
Approval Date 9/24/98

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 questions 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.

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:

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?

YES / ___ / NO / X /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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?

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9 (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 Pepcid AC (famotidine) Nonprescription Tablets

NDA # 19-462, 19-510, 19-527, 20-249, & 20-752 Pepcid (famotidine) Tablets, Injection, Oral Suspension, and Injection Premixed, respectively.

NDA # 19-752 Pepcid RPD (famotidine) Rapidly Disintegrating 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 9. 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 / X / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

- (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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /X/ NO /___/

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?

<p>Investigation #1</p> <p>IND # _____ YES /___/</p>	<p>NO /___/ Explain: _____</p> <p>_____</p> <p>_____</p>
<p>Investigation #2</p> <p>IND # _____ YES /___/</p>	<p>NO /___/ Explain: _____</p> <p>_____</p> <p>_____</p>

(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?

<p>Investigation #1</p> <p>YES /___/ Explain _____</p>	<p>NO /___/ Explain _____</p>
--	-------------------------------

Investigation #2

YES /___/ Explain _____

NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

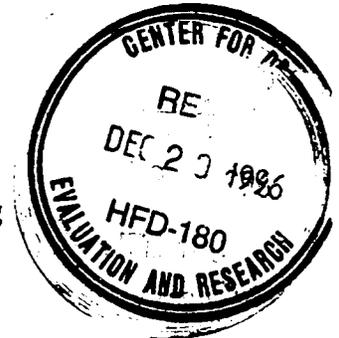
 / S /
Signature of preparer
Title: Regulatory Project Manager
Date 9/25/98

 / S /
Signature of Division Director
Date 9-25-98

cc:
Archival NDA 20-801
HFD-180/Division File
HFD-180/CSO/M. Folkendt
HFD-85/Mary Ann Holovac

December 18, 1996

Stephen B. Fredd, M.D. - Director
Division of Gastrointestinal and Coagulation
Drug Products, HFD - 180, Room 6B45
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 20-801: Nonprescription Famotidine Chewable Tablets 10mg
(famotidine)**

Dear Dr. Fredd:

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 Nonprescription Famotidine 10mg Chewable Tablets.

PEPCID AC® Chewable Tablets is expected to be an effective alternate dosage form for the approved indications because it has been demonstrated to be bioequivalent to Nonprescription Famotidine (PEPCID AC®) 10mg tablets. In this regard reference is made to the approved NDA 20-325 for non-prescription famotidine 10mg tablets.

This application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations. It consists of a complete "archival" copy (blue binders), comprising thirteen volumes, and five "review" copies as described in the Statement of Organization which is attached to this letter.

In accordance with the Prescription Drug User Fee Act of 1992, two checks were sent to the Food and Drug Administration, P.O. Box 3606909, Pittsburgh, PA on December 13, 1996.

Pursuant to 21 CFR 314.50(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.

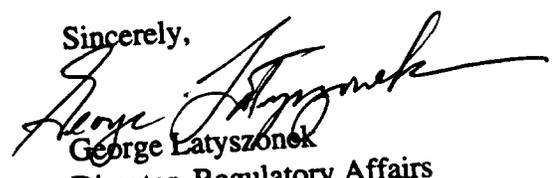
Merck affirms that all sites listed in this application to support the manufacturing packaging and labeling of Nonprescription Famotidine 10mg Chewable Tablets for the market are available for pre-approval inspection at the time of this submission.

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 this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

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 from Merck & Co., Inc.

Questions concerning this application should be directed to George Latyszonek (215/233-7152) or, in my absence, to Edwin L. Hemwall, Ph.D. (610/397-2306).

Sincerely,



George Latyszonek
Director, Regulatory Affairs
Johnson & Johnson • Merck Consumer
Pharmaceuticals Company

APPEARS THIS WAY
ON ORIGINAL

Attachment

Federal Express #1

Desk Copy (Letter and Patent Information Only)

Mr. George Scott, HFD-84, Room 8B37 Federal Express #2

Desk Copy (Item 3 only): Philadelphia District Office
Food and Drug Administration
U.S. Customs House, Room 900
2nd and Chestnut Sts.
Philadelphia, PA 19106-2973

APPEARS THIS WAY
ON ORIGINAL

Federal Express #3

APPEARS THIS WAY
ON ORIGINAL

December 13, 1996

Re: PEPCID AC Chewable Tablets
Famotidine
NDA 20-801
Information required in accordance with 21 CFR § 355 (b)(1)

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act 21 USC 355 (b)(1), attached hereto please find patent information for the above-identified application.

Attached item 13 lists two patents. The undersigned declares that U.S. Patent No. 4,283,408 covers the formulation, composition, and/or method of use of the product which is the subject of this application for which approval is being sought. The undersigned further declares that U.S. Patent No. 5,075,114 covers the formulation, composition, and/or method of use of the product which is the subject of this application for which approval is being sought.

Specifically, the undersigned declares that U.S. Patent No. 4,283,408, having an expiration date of October 15, 2000, and owned by Yamanouchi Pharmaceutical Co., Ltd., claims the drug substance and drug product which is the subject of this application. The undersigned further declares that U.S. Patent No. 5,075,114, having an expiration date of February 24, 2008, and owned by McNeil PPC, Inc., claims the drug product which is the subject of this application.

A claim of patent infringement could be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product of this application for which approval is sought.

Very truly yours,



Richard S. Parr

NDA: 20-801
Famotidine
Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

- | | |
|--|---|
| 1. Active Ingredient | Famotidine |
| 2. Strengths | 10 mg |
| 3. Trade Name | PEPCID AC Chewable Tablets |
| 4. Dosage form
Route of Administration | Tablet
Oral |
| 5. Applicant Firm Name | Merck Research Laboratories |
| 6. NDA Number | 20-801 |
| 7. Approval Date | - |
| 8. Exclusivity-Date First
ANDA Could be Submitted | 3 years from NDA approval date |
| 9. Applicable Patent Number* | 4,283,408 Expires: October 15, 2000
5,075,114 Expires: February 24, 2008 |

Patent expiration dates determined by 35 USC 154(c) enacted pursuant to the General Agreement of Tariffs and Trade (GATT), [Pub. L. No. 103-465 (H.R. 5110), signed December 8, 1994, effective January 1, 1995].



Food and Drug Administration
Rockville MD 20857

NDA 20-801

Merck Research Laboratories
Attention: George Latyszzonek
Sumneytown Pike, BLA-20
West Point, PA 19486

MAR - 4 1998

Dear Mr. Latyszzonek:

We acknowledge receipt on February 6, 1998 of your February 5, 1998 amendment to your new drug application (NDA) for nonprescription Pepcid® AC Acid Controller (famotidine) Chewable Tablets, 10 mg.

This amendment contains additional information, submitted in response to our December 10, 1997 approvable letter, concerning the bioequivalence, Chemistry, Manufacturing, and Controls, and revisions to the submitted draft labeling.

We consider this a complete class 2 response to our December 10, 1998 letter. Therefore, the user fee goal date is August 6, 1998.

If you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

/S/ 3/4/98

Michael Folkendt
Project Manager
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc: Original NDA 20-801
HFD-180/Div. Files
HFD-180/CSO/M.Folkendt
DISTRICT OFFICE

Drafted by: mf/March 4, 1998
Final: 3/4/98
filename: 20801803.ACK

ACKNOWLEDGEMENT (AC)

Folkendt

NDA 20-801

JAN 14 1997

Merck Research Laboratories
Attention: George Latyszonek
Sumneytown Pike, BLA-20
West Point, PA 19486

Dear Mr. Latyszonek:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: **Pepcid AC® Acid Controller™ (famotidine) Non-prescription Chewable Tablets, 10 mg**

Therapeutic Classification: **Standard**

Date of Application: **December 18, 1996**

Date of Receipt: **December 19, 1996**

Our Reference Number: **20-801**

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 17, 1997 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

Michael Folkendt
Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20801 Trade Name: PEPCID AC (FAMOTIDINE) 10MG
 Supplement Number: Generic Name: FAMOTIDINE
 Supplement Type: Dosage Form: TAB
 Regulatory Action: AP Proposed Indication: Treatment of Heartburn, Acid Indigestion, and Sour Stomach. Prevention of meal-induced heartburn, acid indigestion, and sour stomach.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?
 ___ NeoNates (0-30 Days) ___ Children (25 Months-12 years)
 ___ Infants (1-24 Months) Adolescents (13-18 Years)

Label Status [Info not filled out]
 Formulation Status [Info not filled out]
 Studies Needed [Info not filled out]
 Study Status [Info not filled out]

APPEARS THIS WAY ON ORIGINAL

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
9/10/98 This NDA provides for a chewable dosage form for OTC Pepcid AC (famotidine, 10 mg). This product is labeled down to 12 years of age.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
MICHAEL FOLKENDT

Signature MS

Date 9/10/98

APPEARS THIS WAY ON ORIGINAL

9/10/98