CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20958	**Trade Name:**	PEPCID (ANTACID/FAMOTIDINE)10/165
Supplement Number:		**Generic Name:**	ANTACID/FAMOTIDINE
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	AE	**Proposed Indication:**	Treatment of Heartburn, associated with acid indigestion and sour stomach

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) X Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

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

COMMENTS:
This NDA provides for a non-prescription drug product. 6-5-2000 This will be labeled for use in 12 years & above. Up until the present time, OTC products containing H2 blockers have only been AP for use in 12 Years & above.

When AP, the AP letter will have the language asking them to submit the pediatric plan.

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

/S/ 6-5-00

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20958	**Trade Name:**	PEPCID ——— (ANTACID/FAMOTIDINE)10/165
Supplement Number:		**Generic Name:**	ANTACID/FAMOTIDINE
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	NA	**Proposed Indication:**	Treatment of Heartburn, associated with 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 (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:
This NDA provides for a non-prescription drug product.

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

/S/ _____ 2/11/99

Signature Date

January 28, 1998

Re: PEPCID
Famotidine/calcium carbonate/magnesium hydroxide
NDA 20-958
Patent information required in accordance with 21 CFR § 314.53

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 Nos. 4,283,408 and 5,229,137 cover 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., and licensed to Merck & Co., Inc., claims the drug substance and drug product which is the subject of this application. The undersigned further declares that U.S. Patent No. 5,229,137, having an expiration date of May 6, 2012, and owned by Brigham & Women's Hospital, and licensed to Merck & Co., Inc., claims the drug product and method of use 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

Attachment

cc: Central Document Room
Center for Drug Evaluation & Research
Food and Drug Administration
Park Bldg. - Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

NDA: 20-958
Famotidine/calcium carbonate/magnesium hydroxide
Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredients	Famotidine, calcium carbonate, magnesium hydroxide	
2. Strengths	10 mg famotidine 800 mg calcium carbonate 165 magnesium hydroxide	
3. Trade Name	PEPCID ——	
4. Dosage form Route of Administration	Tablet Oral	
5. Applicant Firm Name	Merck Research Laboratories	
6. NDA Number	20-958	
7 Approval Date	-	
8. Exclusivity-Date First ANDA Could be Submitted	3 years from NDA approval date	
9. Applicable Patent Number*	4,283,408 5,229,137	Expires: October 15, 2000 Expires: May 6, 2012

NDA 20-958: PEPCID
(Famotidine/calcium carbonate/magnesium hydroxide)

Patent No.	*Patent Claim*	*Exp Date*	*Owned By*	*Licensee-Address*	*Licensee US Contact-Address*
5,229,137	composition method of use	5/6/12	Brigham & Women's Hospital	Brigham & Women's Hospital 75 Francis Street Boston, MA 02115	Attn: Brian Hicks Director Ventures Department Brigham & Women's Hospital 75 Francis Street Boston, MA 02115
4,283,408	active ingredient	10/15/00	Yamanouchi Pharmaceutical Co., Ltd.	Merck & Co., Inc. One Merck Dr. Box 100 Whitehouse Station, NJ 08889-0100	Richard Parr Merck & Co., Inc. 126 E. Lincoln Ave. RY 60-30 Rahway, NJ 07065-0900

Patent Submission Suggested Format

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information please refer to 21 C.F.R. 314.53.

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA # 20-958

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: PEPCID
- Active Ingredient(s): famotidine, calcium carbonate, magnesium hydroxide
- Strength(s): 10 mg famotidine, 800 mg calcium carbonate, 165 mg magnesium hydroxide
- Dosage Form: Tablet
- Approval Date: Pending

A. This section should be completed for each individual patent

This format repeats to allow up to three patents. If there are additional patents, please copy and attach.

U.S. Patent Number: 4,283,408

Expiration Date: October 15, 2000

Type of Patent–Indicate all that apply:

1. Drug Substance(Active Ingredient) X Y ___N
2. Drug Product(Composition/Formulation) X Y ___N
3. Method of Use ___Y ___N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent:_____

Name of Patent Owner: Yamanouchi Pharmaceutical Co., Ltd.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): MERCK & CO., INC.

U.S. Patent Number: 5,229,137

Expiration Date: May 6, 2012

Type of Patent--Indicate all that apply:

1. Drug Substance(Active Ingredient) ___Y ___N
2. Drug Product(Composition/Formulation) _X_Y ___N
3. Method of Use _X_Y ___N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent: Relief of heartburn, acid indigestion and sour stomach

Name of Patent Owner: Brigham Women's Hospital

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

U.S. Patent Number: 5,817,340

Expiration Date: December 1, 2012

Type of Patent--Indicate all that apply:

1. Drug Substance(Active Ingredient) ___Y ___N
2. Drug Product(Composition/Formulation) _X_Y ___N
3. Method of Use ___Y ___N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent: _____

Name of Patent Owner: McNeil - PPC, Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

This format repeats to allow up to three patents. If there are additional patents, please copy and attach.

The undersigned declares that the above stated United States Patent Number 5,229,137 covers the composition, formulation and/or method of use of PEPCID . ——— (name of drug product). This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- _X_the subject of this application for which approval is being sought.)

The undersigned declares that the above stated United States Patent Number 5,817,340 covers the composition, formulation and/or method of use of PEPCID (name of drug product). This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- _X_the subject of this application for which approval is being sought.)

The undersigned declares that the above stated United States Patent Number _____ covers the composition, formulation and/or method of use of _____(name of drug product). This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- ___the subject of this application for which approval is being sought.)

Signed:
Date: October 29, 1998
Title (optional): Senior Patent Attorney
Telephone Number (optional): (732) 594-4958

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the ***The Orange Book,*** a deskcopy should be submitted to:

Mailing address: **(US Mail)**

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OR

Location address: (for FedX deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the ***The Orange Book***.

Previous Page

EXCLUSIVITY SUMMARY for NDA # 20-958 SUPPL # _____

Trade Name Pepcid Complete Chewable Tablets
Generic Name [famotidine 10 mg/antacid (calcium carbonate 800 mg, and aluminum hydroxide 165 mg)].
Applicant Name Merck Research Laboratories HFD-180
Approval Date October 15,2000

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 / X / NO /___/

      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? (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 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 /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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 /X/ NO /___/

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

NDA # 19-462 Pepcid Tablets

NDA # 19-510 Pepcid Injection

NDA # 19-527 Pepcid for Oral Suspension

NDA # 20-249 Pepcid Injection Premixed

NDA # 20-752 Pepcid RPD Orally Disintegrating Tablets

NDA # 20-325 Pepcid AC Acid Controller Tablets

NDA # 20-801 Pepcid AC 10mg Chewable Tablets

NDA # 20-902 Pepcid AC Coated Tablets

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 /___/ 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 /__X__/ 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 /__X__/

   (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 /X/

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 106: single-dose, at-home-daytime onset & duration of relief 26

Investigation #2, Study 109: single-dose, in-clinic-evening response to provocative meal 33

Investigation #3, Study 110: multiple (4)-episode, at-home onset & duration of relief

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 /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /_X_/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #1, Study 106: single-dose, at-home-daytime onset & duration of relief 26

Investigation #2, Study 109: single-dose, in-clinic-evening response to provocative meal 33

Investigation #3, Study 110: multiple (4)-episode, at-home onset & duration of relief

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, i) 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 /X/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /X/ 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 _____

_____

_____

(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 /X/

If yes, explain: _____

_____

_____

/S/

Signature of Preparer

Title: **Project Manager**

10/13/00

Date

/S/

Signature of Office of Division Director

10-18-00

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and
Coagulation Drug Products
Attention: Division Document Room, Rm 6B2
5600 Fishers Lane
Rockville, Maryland 20857

Memorandum

To: George Latyszonek
Director, Regulatory Affairs
Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004

From: Paul E. Levine, Jr.
Regulatory Project Manager

Date: 02/02/00

Re: Dissolution questions (NDA 20-958, Pepcid Complete)

Please find below questions presented by the Biopharm reviewer in response to October 5, 1999, request to use apparatus III instead of apparatus II as recommended by the Division in the February 19, 1999, Not Approvable letter.

1.) Provide dissolution data using whole tablet, 100 rpm, apparatus II, 900 ml of acetate, at pH 4.5, without the SLS surfactant

2.) Provide dissolution data using apparatus III with less than —

3.) Provide a rationale for using 900 ml of acetate medium with apparatus III. Indicate whether data was acquired using volumes intermediate to 250 ml and 900 ml.

4.) Clarify the results obtained using whole tablets using 0.1M HCl as the medium. These results are found in table 10, page 26, volume 1. (Clarification refers to % dissolved - how much is famotidine and its degradents in the total % dissolved at each of the sampling time points).

1-1

CSO/Folkerdt
C-91

Memorandum Addendum

Department of Health and Human Services
Public Health Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Tuesday, April 07, 1998

To: Mei-Ling Chen, Ph.D.
John Hunt

From: Alfredo R. Sancho, Ph.D. - Reviewer

Re: 45-Day Pre-filing Meeting for NDA 20-958, Pepcid —— (famotidine/antacid combination) Chewable Tablet.

COMMENTS FOR THE SPONSOR (CONT.')

4. It is noted that in this submission (NDA 20-958, Pepcid ——) there is no study in which the 10 mg Famotidine and the Antacid were given concurrently but in separate tablets. It is also noted that in the submission NDA 20-235, Volume 1.10, Pages 251-321, Study #021 (Pepcid AC, 10 mg tablet), there was such a study, to evaluate the effect of an antacid given concurrently with 10 mg Famotidine. Please inform us of any other studies, completed or in process, that have a protocol in which an antacid is given with Famotidine concurrently in the same patient.

RECOMMENDATION/S

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, is of the opinion that NDA 20-958 may be filed by the sponsor. However, Comments No. 1 - 4 should be communicated to sponsor as soon as possible.

/S/

Alfredo R. Sancho, Ph.D.
Pharmacologist/Pharmacokinetic Reviewer
Gastrointestinal Medications Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-180 NDA 20-958 (1x); DIV.FILE (1x); SANCHO (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

Jolkendt

Memorandum

Department of Health and Human Services
Public Health Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

APR - 7 1998

Friday, April 03, 1998

To: Mei-Ling Chen, Ph.D.
John Hunt

From: Alfredo R. Sancho, Ph.D. - Reviewer

Re: 45-Day Pre-filing Meeting for NDA 20-958, Pepcid —— (famotidine/antacid combination) Chewable Tablet.

SUMMARY

Pepcid —— is an OTC compound for the treatment and prevention of heartburn, acid indigestion, and sour stomach. The proposed marketable tablet (1750 mg total weight) is chewable and contains *10 mg famotidine*, *800 mg calcium carbonate*, and *165 mg magnesium hydroxide*. Sponsor states that "The amount of antacid in each tablet provides 21.5 mEq of acid-neutralizing capacity (ANC), which is within the range of doses typically used in OTC antacid products for the treatment of intermittent heartburn." It is also stated in the submission that this product is "a combination product for treating heartburn which would be faster acting than famotidine 10 mg alone, while retaining the duration of action associated with famotidine 10 mg. The principal sponsor, Merck Research Laboratories has also requested a categorical exclusion from the requirements to prepare an Environmental Assessment. The proposed tablet estimated concentration at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below 1 part per billion (PPB).

OVERVIEW

1. Background

Pharmacokinetics

Famotidine being an approved drug (NDA 20-235), its pharmacokinetic profile in healthy subjects and target population is adequately known. From 5 to 40 mg, famotidine has linear pharmacokinetics and has a "moderately-short" half-life. Following I.V. or P.O. administration, $t_{1/2}$ average is 2.8 hrs. in healthy young subjects and 4 hrs. in healthy elderly subjects. Famotidine is not extensively protein-bound yet shows extensive intersubject variation in plasma and renal clearance.

Drug-Drug interactions

No known drug-drug interactions have been identified with famotidine alone, through human, animal and in-vitro studies. Although not directly studied, concomitant administration of antacids may reduce the absorption of other drugs, such as tetracyclines, and iron supplements.

No studies addressing potential interactions between the components (e.g. antacid and famotidine) of the proposed compound were conducted.

2. *Submission studies*

Bioavailability

Three single-dose, two period crossover studies in healthy subjects were performed to characterize the bioavailability of famotidine 10 mg administered in the proposed formulation. In these studies, 120 ml of water was ingested after the proposed or to-be-marketed tablet was chewed and swallowed. The following famotidine 10 mg PK parameters -in the proposed formulation- were calculated from the obtained data sets: Mean Plasma Concentration Profile, $AUC_{0\text{-}24hrs.}$ (ng*hr/ml), C_{max} (ng/ml), and T_{max} (hr.). The sponsor's rationale for an $AUC_{0\text{-}24\ hrs.}$ is that in previously extrapolated $AUC_{24\ hrs.\text{-}\infty}$ the results were found to be small for a dose of 10 mg Famotidine.

Pharmacodynamics

An open-label, randomized, four-period, crossover study was conducted to determine the pharmacodynamic profile of the proposed tablet. A total of 23 healthy subjects received each of the following four treatments 1 hour after eating a high-fat evening meal: 1)10 mg famotidine film-coated-tablet (FCT), 2)the proposed tablet, 3)1 chewable antacid 21.5 mEq ANC tablet, and, 4)1 chewable placebo tablet. All treatments were administered with 60 ml of water. An antimony probe was used to measure esophageal and gastric pH from 1 hour before the meal until the next morning, approximately 8 hours.

Phase IIb protocol 104 was conducted to asses or evaluate the onset and duration of heartburn relief in an at-home scenario. This particular protocol was a double-blind, randomized, single-dose, parallel design, four-site study that randomized 329 frequent heartburn sufferers to 1 of 4 treatment regimens: 1)FACT, the proposed compound, 2)FAM, famotidine 10 mg, 3)AA, antacid 21.5 mEq, and, 4)PBO, placebo. Patients ate an evening meal that would regularly cause heartburn. When subjects developed heartburn of a severity they would usually treat, they took the study medication with 60 ml of water. Subjects rated their heartburn and the relief, if any at 10 minute intervals for up to 2 hours post-dose.

Phase III studies were to determine if FACT has a faster onset of symptom control than famotidine 10 mg FCT, and to determine whether FACT provides a longer duration of relief than antacid 21.5 mEq. Three different heartburn models were employed, yet all three trials were randomized, double-blind, double-dummy, multi-center, factorial, parallel design with 4 equal-sized treatment groups: 1)FACT, 2)Famotidine 10 mg FCT, 3)antacid 21.5 mEq, and, 4)PBO. The three studies enrolled subjects aged 18 years or older who reported heartburn at least three times per week that was generally relieved with antacids or nonprescription acid reducers. Specifically the studies were: 1)Multiple-Episode Study Protocol 110; 2)Evening Heartburn Study Protocol 109, and, 3)Daytime Heartburn Study Protocol 106.

A Use Study, Protocol 111, was an open-label, in-home use trial that enrolled 496 heartburn sufferers who were randomly recruited at 10 different shopping malls. After signing an informed consent, they received a bottle containing 30 FACT tablets and a draft panel label. Subjects were instructed to read the label and use the product as needed over the following 2 weeks. Each usage occasion was to be recorded in a diary that was to be mailed back to the coordinating site after the 2-week period. A total of 373 subjects returned the diary before the end of the study cutoff date and were included in the data analysis.

	FACT	Famotidine 10 mg FCT	Antacid ?1.5 mEq	Placebo PBO
Subjects				
Single-dose studies	85	86	24	25
Patients				
Single-dose studies	662	667	662	668
Four-dose study	307	311	309	307
Use study (≤30 doses)	465	0	0	0
Total number of individuals	1519	1064	995	1000

Clinical Studies

In the present submission there are 9 (nine) clinical studies conducted for this compound.

Protocol No.	Type	Title
095	Clinical Pharmacology	Open-label, crossover, single-dose study to determine ***bioequivalence*** of compound and famotidine FCT in fed state.
096	Clinical Pharmacology	Open-label, crossover, single-dose study to determine absolute ***bioavailability*** of famotidine administered in proposed formulation.
098	Clinical Pharmacology	Open-label, crossover, single-dose ***pharmacodynamic*** study measuring esophageal and gastric pH after administration of proposed compound components.
101	Clinical Pharmacology	Open-label, crossover, single-dose study to determine ***bioequivalence*** of proposed compound and famotidine FCT in fasting state.
104	Phase IIb	Double-blind, pilot, factorial, single-dose ***at-home evening*** heartburn study.
106	Phase III	Double-blind, factorial, single-dose ***at-home daytime*** heartburn study to assess ***onset and duration of relief***.
109	Phase III	Double-blind, factorial, single-dose ***in-clinic evening provocative meal*** study to assess ***onset and duration of relief***.
110	Phase III	Double-blind, factorial, ***multiple (4)-episode***, ***at-home*** study to assess ***onset and duration*** of heartburn relief.
111	Use Study	Open-label, uncontrolled, ***multiple-dose***, pattern of use study.

Assay Method/s

Determination of famotidine in human plasma was done using a ——— with ultraviolet (UV) absorbance detection. Absolute bioavailability included a solid phase extraction and a protein precipitation with ——— Both methods had a Limit of Quantitation (LOQ) o

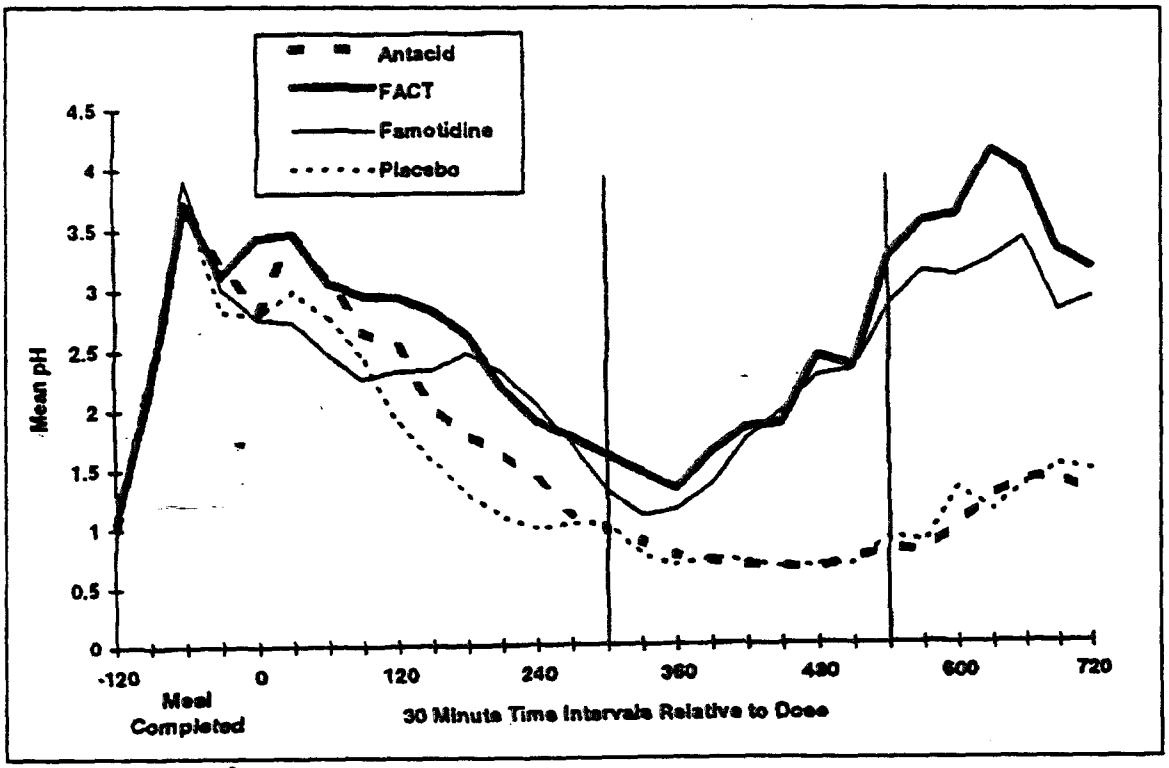
Safety

Safety was addressed as any clinical adverse experience from all subjects that were enrolled in the nine FACT studies. The same chewable formulation of FACT was used in all nine studies. All adverse experiences were collected through spontaneous patient reporting. The reporting was done in-person for all studies except for the Use Study Protocol 111, in which subjects had to call a central telephone number to report any adverse experiences, since there was no follow-up visit.

COMMENTS FOR IN-HOUSE

Rationale for product

Single dose of antacid alone and famotidine 10 mg alone relieve heartburn more effectively than placebo. Although both agents are believed to act by reducing the intraluminal acidity, their mechanisms of action and pharmacodynamic profiles differ substantially. Antacids are believed to work rapidly by neutralizing intraluminal acid on contact. Their duration of action is limited by physiological clearing mechanisms. Famotidine reduces gastric acid production via competitive antagonism of the histamine H_2 receptor. Famotidine 10 mg is believed to require a longer time to onset of pharmacodynamic effect than antacid, but famotidine has an appreciably longer duration of effect than antacids. These differences suggest that a combination of famotidine and antacid in 1 tablet would potentially offer the benefits of more rapid relief of symptoms than famotidine alone, and a longer duration of heartburn relief than antacid alone, as seen in the following chart, an excerpt from the sponsor's submission (page C-10, Figure C-2). In this figure the gastric pH was measured and plotted at each one half hour intervals for each of the treatment regimens from two hours prior to dosing to 12 hours post-dose.



Rationale for dosage

A reasonably size chewable tablet ——— containing famotidine in its approved non-prescription dose (10 mg) was achieved. Within this same size tablet enough $CaCo_3$-$Mg(OH)_2$ was introduced to provide 21.5 mEq ANC, an amount within the range for antacid products.

Component-Component interactions

There may be a difference in the active ingredients of the proposed marketable tablet (FACT) PK parameters (*e.g.* Famotidine absorption rate; or, Antacid efficacy onset and duration) when given in the same formulated tablet as compared to when given concurrently but in separate tablets. These effects are hinted to by the results of one bioavailability study (Protocol 101) in which subjects were dosed in a fasted state. The calculated T_{max} for FCT (10 mg Famotidine alone) was 1.8 hours, which was statistically different than that for FACT (sponsor proposed marketable tablet) 2.4 hours. In this case, the observed T_{max} difference for Famotidine from FACT may be due to the presence of the antacid in the gastrointestinal lumen, which may have changed the characteristics of the gastrointestinal pH and/or lining, hence possibly affecting the absorption rate of Famotidine. Additionally, the T_{max} difference may be the result of formulation and/or manufacturing process difference for the two tablets (*i.e.* FCT and FACT), which resulted in different disintegration or desolation characteristics between the tablets. Under CFR 21, Part §320.25.g.1 the following is stated:

> *"Generally, the propose of an in vivo bioavailability study involving a combination drug product is to determine if the active drug ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations."*

In essence, in this submission, it is noted that neither the clinical studies nor the bioavailability studies had a treatment where the 10 mg Famotidine tablet and the Antacid tablet were given concurrently. The four different regimens to which the subjects and/or patients were subjected to in these studies were: FACT (10 mg Famotidine + 21.5 mEq ANA), FCT (10 mg Famotidine), ANC (21.5 mEq), PBO.

The above issues were brought up in the 45-day filing meeting held on March 31st, 1998 (PKLN 6B-45), where HFD-180's staff also noted that the studied antacid tablet may not be a commercially available product. It was raised for the Antacid tablet (if its not a commercial product), that it should be determined if it would meet the OTC monograph, such that it could qualify as a marketable product. Regarding the need to have information/data on FCT and the Antacid tablet given separately but concomitantly, it was decided that the reviewing Medical Officer and OCPB staff would need further discussions. It generally was felt not to be a filing issue, knowing that there is safety and efficacy data provided on the combination tablet. If such information/data are determined to be needed it might be considered as a Phase IV option. It was noted in previous meeting discussions between HFD-180's previous Division Director, Dr. Fredd, that the emphasis was on comparing FACT to FCT and ANC given separately and not simultaneously to the same subjects.

COMMENTS FOR THE SPONSOR

1. Being that the proposed marketable tablet (Pepcid ——— is chewable; were the subjects and/or patients in the bioavailability and clinical studies instructed on how long to chew the

tablet before swallowing? Depending on how well the tablet is chewed before swallowed, it may affect the absorption rate of Famotidine.

2. Please identify the antacid product/s given to the subjects and patients in the various bioavailability and clinical studies. The ingredients -active and inactive- in the independently used antacids in these studies need to be compared to the antacid portion of the proposed marketable tablet (FACT) in this submission.

3. In the submission there is a brief explanation of the rationale for why AUC is only calculated up to the 24 hour post-dose time point. Specifically, it is stated that "*Extrapolated 24 hour-to-infinity [AUC]s were previously found to be small following the administration of 10 mg Famotidine [Ref.8]. As a result, the extrapolation was not performed for Protocols 095, 096, and 101.*" Further justification needs to be given to not calculate the AUC 24 hour-to-infinity, as is customary.

RECOMMENDATION/S

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, is of the opinion that NDA 20-958 may be filed by the sponsor. However, Comments No. 1 - 3 should be communicated to sponsor as soon as possible.

/S/

Alfredo R. Sancho, Ph.D.
Pharmacologist/Pharmacokinetic Reviewer
Gastrointestinal Medications Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-180 NDA 20-958 (1x); DIV.FILE (1x); SANCHO (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

MINUTES OF MEETING

DATE: October 6, 2000
ATTENDEES: Bronwyn Collier, Associate Director for Regulatory Affairs, ODE III
Susan Lange, Associate Director for Regulatory Affairs, ONDC
Dr. Charles Hoiberg, Deputy Director, ONDC
Dr. John Gibbs, Director, DNDC II
Michael Adams, Chemistry Reviewer, Division of Gastrointestinal and Coagulation Drug Products
SUBJECT: NDA 20-958; Pepcid Complete

Purpose of Meeting: To discuss the conclusions reached in chemistry review #3 dated October 6, 2000.

Discussion: Mr. Adams indicated in his chemistry review #3, 5 comments/requests that should be conveyed to the sponsor prior to approval. Each comment was evaluated as to whether it constituted an approvability issue that would have to be addressed by the sponsor before the application could be approved.

Conclusions:
1. None of the comments/requests constitute approvability issues. The application can be approved from the standpoint of chemistry.
2. Ms. Collier will convey two requests to the sponsor regarding chromatograms identifying the _____ and clarification of the post-marketing commitment concerning methods validation. The sponsor will be informed that these requests are not approvability issues.
3. The balance of the comments/requests in chemistry review #3 will not be conveyed to the sponsor.

/S/ 10/12/00
Meeting recorder
Bronwyn Collier, ADRA ODE III

/S/ 10/12/00
Meeting Chair
Dr. Charles Hoiberg, Deputy Director, ONDC

CC:
Archival NDA 20-958
HFD-180/Division File
HFD-180/P.Levine, M.Adams, L.Zhou, L.Talarico
HFD-800/C.Hoiberg, S.Lange
HFD-820/J.Gibbs

MINUTES OF MEETING

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180

MEMORANDUM

Date: June 18, 2000

From: Steven Aurecchia, MD /S/ 6/18/00
Dep. Director, DGICDP

Subject: NDA 20-958 (Pepcid ® Complete)

To: File

NDA 20-958 is intended to support the OTC marketing of a fixed combination of famotidine and antacid for the relief of heartburn, indigestion and sour stomach. Both the antacid and 10 mg. famotidine components are currently approved OTC products for this indication. The pharmacologic rationale for the new product is that the combination should provide more rapid relief than famotidine alone and longer duration of relief than antacid alone. No new marketing claim(s) are proposed, however, with respect to either the rapidity of onset or the duration of symptomatic relief.

The application was initially submitted in February 1998 with three similar clinical trials that showed mixed results for the efficacy of the combination. No increased safety risk was observed nor did the bioavailability of the famotidine component appear to be compromised to any clinically relevant extent. An approvable action was taken on February 19, 1999, with a request for a confirmatory clinical trial. Study #127, the subject of the present submission, was submitted in response to that action.

As noted in the statistical review, Study #127 may not have achieved its stated objectives. The primary analyses for onset of relief and duration of relief utilized a complex statistical model that involves multiple assumptions and interrelated parts. The clinical study report did not adequately address the validity of these assumptions nor was the robustness of the model tested relative to similar models or other analytical methods.

We will therefore take an approvable action. This will afford the sponsor an opportunity to address the statistical deficiencies. The remaining CMC deficiencies, to which the sponsor has recently responded, will also be reviewed during the next cycle.

CC: NDA Arch. 20-958
HFD-180/L Talarico
HFD-180/S Aurecchia
HFD-180/H Gallo-Torres
HFD-180/S Kress
HFD-180/A Kacuba
HFD-560/C Ganley
HFD-560/D Keravich

C80/Folkendt

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 27, 1998
Time: 9:30 - 10:30 a.m.
Location: Conference Room
Merck Office Building
5615 Fishers Lane, Suite 125
Rockville, MD 20852

Application: NDA 20-958
Drug: Pepcid —— (famotidine/antacid combination) Tablets

Type of Meeting: Other (CANDA training).

Meeting Recorder: Michael Folkendt, Project Manager, HFD-180

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
John R. Senior, M.D.; Medical Officer
Michael Folkendt; Project Manager

External Constituent Attendees and titles:

Merck Research Laboratories:
George Latyszonek; Director, Regulatory Affairs
Daniel F. Orfe; Senior Systems Associate, Electronic Regulatory Submission Development
Margo E. Herron; Associate Director, Regulatory Agency Affairs

Background:

NDA 20-958, submitted on February 20, 1998, provides for a famotidine/antacid combination chewable tablet for the treatment of heartburn. In addition to the traditional paper copy of the NDA, the firm provided the complete application on computer (CANDA or Computer Assisted NDA) as Adobe Acrobat indexed image files (PDF). In late July 1998, the Medical Officer, Dr. John Senior, indicated that he will soon begin his in-depth review of this application and requested that the firm train him on the use of the submitted CANDA. The training session was scheduled on August 4, 1998 and training manuals for the CANDA was submitted on August 11, 1998.

Meeting Objectives:

To provide training on the use of the submitted CANDA.

Discussion Points:

1. The CANDA files reside on a network server. Once access is granted to a reviewer, a windows desktop icon to launch Adobe Acrobat Exchange and the NDA table of contents file [NDATOC.PDF] will be installed on the reviewer's computer. The complete CANDA for this application is ~370 Megabytes and can reside on a single CD. The firm has offered to submit this CD if requested.

2. The training session allowed the reviewer to learn and practice the skills necessary to effectively use the CANDA. These skills included:

   - Using the index to navigate around the system.
   - Viewing specific documents.
   - Copying text and objects (figures and tables) from the CANDA and pasting into an MS Word document.
   - Using the search and find capabilities of the system and the differences between the search and the find capabilities.
   - Printing specific parts of the CANDA.

3. In response to Dr. Senior's request that the clinical efficacy data be provided in MS Access format in addition to the submitted SAS format, the firm stated that the data was actually provided as SAS transport files. They will inquire whether MS Access can import SAS transport files.

/S/

Minutes Preparer 9/9/98

Concurrence: JR Senior 14 Sep 98

cc: Archival NDA 20-958
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/CSO/M.Folkendt

Drafted: mf 9/8/98
Finaled: 9/9/98

MEETING MINUTES

CSO/Folkendt

MEMORANDUM OF 45-DAY FILING MEETING

March 31, 1998

Application Number: NDA 20-958

Drug: **Non-prescription Pepcid® —— [famotidine, 10 mg/antacid (calcium carbonate, 800 mg; magnesium hydroxide, 165 mg) combination] Chewable Tablets**

Attendees:

Lilia Talarico, M.D.; Director, HFD-180
Michael Folkendt; Project Manager, HFD-180
John Senior, M.D.; Clinical Reviewer, HFD-180
Eric Duffy, Ph.D.; Chemistry Team Leader, HFD-820
W. Mike Adams, M.S.; Chemistry Reviewer, HFD-820
John Hunt; Biopharmaceutical Team Leader , HFD-870
Alfredo R. Sancho; Biopharmaceutical Reviewer, HFD-870
A.J. Sankoh, Ph.D.; Acting Statistical Team Leader, HFD-720
Mushfiqur Rashid, Ph.D.; Statistical Reviewer, HFD-720
Helen Cothran; Team Leader, HFD-560 (via phone)
Rosemary Cook; Supervisory CSO, HFD-560
Albert Rothschild; Project Manager, HFD-560 (via phone)
Mel Lessing; Intadisplinary Scientist, HFD-560 (via phone)

BACKGROUND

This application provides for a chewable combination tablet containing famotidine, 10 mg, and an antacid (calcium carbonate, 800 mg, and magnesium hydroxide, 165 mg; providing 21 mEq of acid neutralizing capacity (ANC)) with a proposed trade name of "Pepcid —— ". The proposed indication is for the relief of heartburn, acid indigestion, and sour stomach. This combination drug product is intended to act faster than famotidine alone and provide longer lasting relief than the antacid component alone. In support of this application, the firm has submitted the results from three Phase III pivotal efficacy trials, 4 Biopharmaceutical studies, 1 Actual Use study, and Chemistry, Manufacturing, and Controls (CMC) information. In addition to the traditional paper copy of this NDA, an electronic version of this application was also submitted. The 60-day filing date for this application is April 21, 1998.

MEETING

I. Filing issues:

1. Administrative:

None that would result in a Refusal-To-File action. However, There were no diskettes submitted with this application. To facilitate the review of this application, the firm should be asked to submit diskettes containing the

labeling and SAS data sets for the statistician. Because this product is for an OTC drug product, the labeling and the Actual Use study will be reviewed by the Division of Over-the-Counter Drug Products per MaPP 6020.5.

2. Clinical:

Dr. Senior stated that there were no clinical filing issues. He stated that the antacid component contains 21 mEq of acid neutralizing capacity (ANC) and that it fulfilled the antacid monograph for an antacid. He also stated that the submitted Phase III studies included a placebo arm. He noted, however, that the proposed indication was not appropriate and may need revision. He requested that the firm submit a diskette containing the efficacy and safety data in Excel Format.

3. Statistical:

Drs. Sankoh and Rashid stated that there were no statistical filing issues. However, they request that the firm submit the efficacy raw data and programs used to generate all the efficacy results on Diskette in SAS format.

3. Chemistry, Manufacturing, and Controls (CMC):

Dr. Duffy stated there are no CMC filing issues, however there are a number of requests of the firm (see attached CMC filing memorandum).

4. Biopharmaceutics:

Drs. Hunt and Sancho stated that the application is fileable from the biopharmacology standpoint. However, they have some requests, including a diskette containing the data from the biopharmacology studies in Excel format (see attached Biopharmacology filing Memorandum).

In addition, Drs. Hunt and Sancho discussed a potential issue concerning a missing arm in the biopharmacology studies. They explained that according to 21 CFR 320.25(g)(1), there should have been an arm in the biopharmacology studies for both the famotidine and the antacid being administered concurrently but as separate tablets. They stated that this requirement is still being discuss within the Division of Pharmaceutical Evaluation II and no decision has been made yet. During the discussion, I informed the team that in several meetings we had with the firm in which representatives from biopharmacology were present, the firm was never informed/reminded of this requirement. I requested that, once a decision is

made, the biopharmacology review address this issue.

5. Actual use study and Labeling issues:

Dr. Neuner stated that the application did have a product Actual Use study and inquired whether or not the firm plans to conduct a Labeling Comprehension study.

6. Advisory Committee Meeting:

The decision as whether or not this application will be discussed at an advisory committee meeting was discussed. Although this application was the first H2/antacid combination drug product, both the antacid component and the famotidine component are currently approved in the OTC market place and there are no apparent safety concerns with this combination. Therefore, it was believed this application should only need to be discussed at the advisory committee meeting if issues arise in the review. The final decision was deferred until the reviews were ongoing and/or completed.

II. Request for information:

It was agreed that the firm will be requested to submit additional information (see attached list of requests).

III. Projected completion of reviews:

After some discussion, the team agreed on the following general date for the completed reviews in order to meet a 10-month goal date:

1. Biopharmacology and Statistical Reviews: by end of August, 1998
2. Clinical and CMC reviews: by the end of September, 1998
3. Labeling and Actual Use Reviews: by the end of October, 1998

IV. Conclusion:

It was agreed that the application will be filed. However, there are numerous requests for additional information (see attached list of requests).

/S/ - 1/29/99

Michael Folkendt
Regulatory Project Manager, HFD-180

cc:
Original NDA 20-958
HFD-180/Div. Files
HFD-180/M.Folkendt
HFD-560/A.Rothschild

drafted: mf/May 8, 1998
final: 1/29/99
filename: 20958A03.MET

MEETING MINUTES

45-Day Pre-filing Meeting for NDA 20-958, Pepcid — (famotidine/antacid combination) Chewable Tablet

COMMENTS FOR THE SPONSOR

1. In this submission, it is noted that neither the clinical studies nor the bioavailability studies had a treatment where the 10 mg Famotidine tablet and the Antacid tablet were given concurrently. The four different regimens to which the subjects and/or patients were subjected to in these studies were: FACT (10 mg Famotidine + 21.5 mEq ANA), FCT (10 mg Famotidine), ANC (21.5 mEq), PBO. Under CFR 21, Part §320.25.g.1 the following is stated:

   > *"Generally, the propose of an in vivo bioavailability study involving a combination drug product is to determine if the active drug ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations."*

   The concern is that the ingredients, inactive and otherwise, of the two separate dosage forms – given concurrently might affect the performance of the active ingredients differently (*e.g.* Famotidine absorption) than when the active ingredients are given together as in the proposed marketable single formulated tablet. Therefore, is there any data available to address properly this concern?

2. Being that the proposed marketable tablet (Pepcid —) is chewable; were the subjects and/or patients in the bioavailability and clinical studies instructed on how long to chew the tablet before swallowing? Depending on how well the tablet is chewed before swallowed, it may affect the absorption rate of Famotidine.

3. Please identify the antacid product/s given to the subjects and patients in the various bioavailability and clinical studies. The ingredients -active and inactive- in the independently used antacids in these studies need to be compared to the antacid portion of the proposed marketable tablet (FACT) in this submission.

4. In the submission there is a brief explanation of the rationale for why AUC is only calculated up to the 24 hour post-dose time point. Specifically, it is stated that "*Extrapolated 24 hour-to-infinity [AUC]s were previously found to be small following the administration of 10 mg Famotidine [Ref.8]. As a result, the extrapolation was not performed for Protocols 095, 096, and 101.*" Further justification needs to be given to not calculate the AUC 24 hour-to-infinity, as is customary.

RECOMMENDATION/S

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, is of the opinion that NDA 20-958 may be filed by the sponsor. However, Comments No. 1 -3 should be communicated to sponsor as soon as possible.

MEMORANDUM

DATE	03/31/98
APPLICATION	NDA 20-958
PRODUCT NAME	Famotidine Antacid Tablets (FACT)
SUBJECT	Filing Meeting Comments

I have reviewed the 5 volumes of CMC information and concluded that there is no justification for a Refuse To File action on this application with regard to the CMC information.

So that the review can be completed, the firm should be requested to provide the following items for information:

1. Regarding the active ingredient, Famotidine:
(a) Provide up to date LOAs for DMFs [redacted] and [redacted] The submitted letters are several years old and refer to annual updates more than one year old. The files are required to include an annual update.

2. Regarding the active ingredient, Calcium Carbonate:
(a) Since this is not a USP material, you should identify the reference standard, provide a detailed description of the preparation of this material, provide data establishing the purity of this material, and describe its impurity profile.
(b) Describe the conditions (temperature and relative humidity) and container/closure systems for storage of this material.
(c) Specify the retest period, provide a stability data to support the proposed retest period, describe the degradation profile for this material, and provide a stability protocol to be used to monitoring the stability of this material over time.

3. Regarding the active ingredient, Magnesium Hydroxide:
(a) Specify the tests performed on each lot of this materials for acceptance.
(b) Since there is no DMF referenced for this material you should describe its manufacture, the in-process controls for this process and its impurity profile.
(c) Describe the conditions (temperature and relative humidity) and container/closure systems for storage of this material.
(d) Specify the retest period, provide a stability data to support the proposed retest period, describe the degradation profile for this material, and provide a stability protocol to be used to monitoring the stability of this material over time.

4. Provide a revised LOA for DMF [redacted] which specifies where the CMC information regarding the [redacted] can be found.

5. Regarding the listed inactive ingredients:
(a) Specify the actual tests performed on each lot of each material for acceptance and provide example COAs for each material from its source.
(b) For each manufacturing site where Purified Water USP is used to prepare drug product or drug product intermediates, briefly describe how the material is obtained and the procedures followed to monitor its chemical and microbiological purity.

6. Specify where product release and stability testing will be performed.

7. Regarding the packaging materials information:
(a) For the [redacted], either provide a description of the composition, manufacture and controls information for this material; provide a LOA to the DMF where this information can be found; or specify where which already referenced DMF provides this information.
(b) Provide the trade names for the [redacted].

Request for additional information:

A. Concerning the clinical/statistical section of the NDA:

1. Please provide the statistical reviewer the efficacy raw data and programs (procedures) used to generate all the efficacy results on diskette in SAS for Windows 6.11 format.

2. Please provide the clinical reviewer the efficacy and safety data on diskette in MS Excel 7.0 format.

3. Please provide the proposed labeling on diskette in either MS Word 6.0 or PDF format.

B. Concerning the CMC section of the application:

1. Regarding the active ingredient, Famotidine:

   (a) Provide up to date LOAs for DMFs [redacted] and [redacted] The submitted letters are several years old and refer to annual updates more than one year old. The files are required to include an annual update.

2. Regarding the active ingredient, Calcium Carbonate:

   (a) Since this is not a USP material, you should identify the reference standard, provide a detailed description of the preparation of this material, provide data establishing the purity of this material, and describe its impurity profile.

   (b) Describe the conditions (temperature and relative humidity) and container/closure systems for storage of this material.

   (c) Specify the retest period, provide a stability data to support the proposed retest period, describe the degradation profile for this material, and provide a stability protocol to be used to monitoring the stability of this material over time.

3. Regarding the active ingredient, Magnesium Hydroxide:

   (a) Specify the tests performed on each lot of this materials for acceptance.

   (b) Since there is no DMF referenced for this material you should describe its manufacture, the in-process controls for this process and its impurity profile.

   (c) Describe the conditions (temperature and relative humidity) and container/closure systems for storage of this material.

   (d) Specify the retest period, provide a stability data to support the proposed retest period, describe the degradation profile for this material, and provide a stability protocol to be

used to monitoring the stability of this material over time.

4. Provide a revised LOA for DMF —— which specifies where the CMC information regarding the —— can be found.

5. Regarding the listed inactive ingredients:

   (a) Specify the actual tests performed on each lot of each material for acceptance and provide example COAs for each material from its source.

   (b) For each manufacturing site where Purified Water USP is used to prepare drug product or drug product intermediates, briefly describe how the material is obtained and the procedures followed to monitor its chemical and microbiological purity.

6. Specify where product release and stability testing will be performed.

7. Regarding the packaging materials information:

   (a) For the —— either provide a description of the composition, manufacture and controls information for this material; provide a LOA to the DMF where this information can be found; or specify where which already referenced DMF provides this information.

   (b) Provide the trade names for the ——

C. Concerning the Biopharmaceuptical section of the NDA:

1. Being that the proposed marketable tablet (Pepcid ——) is chewable; were the subjects and/or patients in the bioavailability and clinical studies instructed on how long to chew the tablet before swallowing? Depending on how well the tablet is chewed before swallowed, it may affect the absorption rate of Famotidine.

2. Please identify the antacid product/s given to the subjects and patients in the various bioavailability and clinical studies. The ingredients -active and inactive- in the independently used antacids in these studies need to be compared to the antacid portion of the proposed marketable tablet (FACT) in this submission.

3. In the submission, there is a brief explanation of the rationale for why AUC is only calculated up to the 24 hour post-dose time point. Specifically, it is stated that "*Extrapolated 24 hour-to-infinity [AUC]s were previously found to be small following the administration of 10 mg Famotidine [Ref.8]. As a result, the extrapolation was not performed for Protocols 095, 096, and 101.*" Further justification needs to be given to not calculate the AUC 24 hour-to-infinity, as is customary.

4. It is noted that in this submission (NDA 20-958, Pepcid ——) there is no study in which the 10 mg Famotidine and the Antacid were given concurrently but in separate tablets. It is also noted that in the submission NDA 20-235, Volume 1.10, Pages 251-321, Study #021 (Pepcid AC, 10 mg tablet), there was such a study, to evaluate the effect of an antacid given concurrently with 10 mg Famotidine. Please inform us of any other studies, completed or in process, that have a protocol in which an antacid is given with Famotidine concurrently in the same patient.

5. Please provide the raw data and pK parameter calculations with table sets for the biopharmaceutical studies on diskette in MS Excel 7.0 format.

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 10, 1997
Time: 1:30 - 3:30 pm
Location: Parklawn Conference Room "J"

Application: IND [redacted]

Type of Meeting: pre-NDA

Meeting Chair: Kathy Robie-Suh, MD

Meeting Recorder: Kati Johnson

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180):

Kathy Robie-Suh, MD, Medical Officer
John Senior, MD, Medical Officer
Kati Johnson, Supervisor, Project Management Staff
Eric Duffy, PhD, Chemistry Team Leader (HFD-820)
Lydia Kaus, PhD, Pharmacokinetics Team Leader (HFD-870)
Rajendra Pradhan, PhD, Pharmacokinetics Reviewer (HFD-870)
A.J. Sankoh, PhD, Biostatistics (HFD-720)

Division of Over-the-Counter Drug Products (HFD-560):

Linda Katz, MD, Deputy Division Director
Helen Cothran, Team Leader
Mary Robinson, Interdisciplinary Scientist
Sakineh Walther, Project Manager
Melvin Lessing, Interdisciplinary Scientist

External Constituent Attendees and titles:

Merck Research Laboratories/Johnson & Johnson Merck Consumer Pharmaceuticals Co:

Gerald McNally, PhD, Pharmaceutical R & D
Ed Hemwall, PhD, Regulatory Affairs
Scott Korn, MD, Clinical Research
George Latyszonek, Regulatory Affairs
Robert Tipping, Biostatistics
Laura Stauffer, Biostatistics
Kenneth Kramer, Chemistry Manufacturing and Controls

Dennis Decktor, PhD Clinical Research
Patrick Ciccone, MD, V.P. Research & Development
Marie Dray, Regulatory Affairs

Background:

Famotidine is currently marketed OTC [under NDA 20-325 (Pepcid AC Acid Controller, approved April 28, 1995] as a film-coated tablet for both the prevention and treatment of heartburn. The firm has requested a pre-NDA meeting to discuss the content and format for a famotidine/antacid combination product for the treatment of heartburn.

Meeting Objective:

The firm provided a list of questions (see below) and is requesting Agency feedback.

Discussion Points (bullet format):

Questions/Discussion

1. Are the format and analytical methods specified in the data analysis plan acceptable?
2. Does the Agency agree with the planned exploratory analysis of "successfully treated" patients (episodes) based on the criterion of adequate relief within 60 minutes that is sustained for the full assessment period?

   The firm was informed that the statistical analysis must demonstrate a benefit of each component in an individual patient and then compare the proportion of patients (having a benefit) receiving Pepcid/AA to the proportion of those patients receiving each component alone. Although the pivotal studies contained different primary efficacy parameters (for evaluation of onset and duration of relief of heartburn), the firm's proposal to define success as that which occurs "within 60 minutes" will not be sufficient to support approval. To the extent possible, the firm will analyze success in shorter time frames of 15 and 30 minutes. The firm was also requested to provide estimates for both the log rank and Wilcoxon rank sum test, and to use both means as well as medians in their survival analysis. Lastly, the firm was requested to analyze for "complete relief" if this information was collected in the studies.

3. Have the plans to consider gender and race in the efficacy analyses been adequately identified?

   With regard to use in children, PEPCID AC Acid Controller is currently labeled for use in pediatric patients at least 12 years of age. This application should also contain a safety database in this population if the firm plans on labeling it for use in pediatric patients.

4. Are the planned presentations of clinical adverse experience data acceptable?

In the open-label, uncontrolled study, there was a dropout rate of approximately 10%. Although the firm plans to assume that there were zero adverse events in this cohort, the Agency requested an analysis which does not make this assumption.

5. Are the plans for electronic submission of clinical documentation acceptable?

The clinical, chemistry, and biopharmaceutics reviewers expressed interest in receiving their respective information in electronic format. The biopharmaceutics team voiced their preference for the final reports contained in their technical section to be in Word Perfect or Word, and the pharmacokinetic data in ASCII format.

6. Given that bioequivalence with famotidine film-coated tablet is established in both fed and fasted states, does the Agency still believe a prevention indication requires additional clinical studies?

The firm must provide results from controlled clinical trials which demonstrates a contribution of each component of Pepcid/AA for the prevention of heartburn.

7. Does the Agency have any comments on format or content of proposed label?

The Agency stated that it was premature to discuss labeling issues at this time.

8. Will the chemistry and manufacturing data for the bottle on stability support use of the alternate-shaped bottle at launch?

Dr. Duffy said that assuming that the data on the initial bottle is acceptable and that there are no stability concerns with the combination product as compared to famotidine as currently marketed, the use of an alternate container at launch may be allowed, with some Phase 4 commitments to submit stability data.

With regard to the interchangeability protocol, Dr. Duffy had the following comments:
• The use of a new resin for the — bottle would be acceptable as long as the type of resin remains constant. DMF authorization for the alternate resin is needed.
• With regard to the innerseal/liner changes, since this has the greatest potential to affect stability, he was not able to determine the acceptability of this proposal given the limited information provided in the background package.
• With regard to the unit-dose contact components, a new resin of the same general type would be acceptable provided it meets the same specifications. The acceptability of a change in the blister/backing/pouch film supplier/location will depend on the composition of the material being changed. For example, we have sufficient information on — to

say that this would be acceptable; however, for other materials, we may not have as much information. Finally, a change in the thickness of the laminate layers or an alternate combination of laminate materials would require a prior approval supplement for implementation.

9. Will the Agency accept additional stability data during the NDA review period without extending the PDUFA date?

The potential for extension of the PDUFA goal date will not be an issue given that the firm plans to submit additional stability data within approximately 4 months of the initial NDA submission.

In conclusions, the firm asked whether this application would be discussed at a joint meeting of the Gastrointestinal and OTC Advisory Committees. Although the Agency does not, at this time, have any particular concerns with the safety of this combination, as this may be the first such approval in its class and other issues may arise during the review process, a final decision can only be made during the review process.

Minutes Preparer: /S/ 1/11/98

Chair Concurrence: _____

cc: Original
HFD-/Div. Files
HFD-/Meeting Minutes files
HFD-/CSO/MFolkendt
HFD-/meeting attendees

Drafted by: Kjohnson 11/14/97
Initialed by: Krobie-Suh 11/17/97 /S/ 1/12/98
AJ Sankoh 11/25/97
Lkatz 12/4/97
Eduffy 1/7/98

MEETING MINUTES

MEMORANDUM OF TELECON

DATE: October 6, 2000

APPLICATION NUMBER: NDA 20-958, Pepcid Complete

BETWEEN:

Name: George Latyszonek, Regulatory Affairs
Phone: 215-273-7152
Representing: Merck Research Laboratories

AND

Name: Bronwyn Collier, Associate Director for Regulatory Affairs, ODE III
Susan Lange, Associate Director for Regulatory Affairs, ONDC

SUBJECT: Information requests; status of application review

Mr. Latyszonek was asked to submit the following to the Pepcid Complete application:

1. a copy of a chromatogram from one of the stability samples that shows that degradates —— and famotidine are detected and adequately resolved by the —— method.
2. A revision to the proposed post-approval commitment to specify the date of completion and mode of submission for the study concerning methods validation. In addition, when the results are submitted, it should include copies of chromatograms from the studies and identification and characterization of a suitable reference standard for degredate —

Mr. Latyszonek was informed that the above requests are not approvability issues. In addition, all reviews except for labeling are complete. The Division of Over-the-Counter Drug Products will convey conclusions from the labeling review.

/S/ 10/12/00

Bronwyn Collier
Associate Director for Regulatory Affairs
ODE III

cc:
Archival NDA 20-958
HFD-180/Division File
HFD-103/RPM/P.Levine
HFD-180/L.Talarico
HFD-800/C.Hoiberg, S.Lange
HFD-180/M.Adams, L.Zhou
HFD-820/J.Gibbs

Drafted by: BC/October 12, 2000
Final: BC/10/12/00
Filename: C:\Data\My Documents\nda\20958telecon2.doc

TELECON

Kacuba

MEMORANDUM OF TELECON

DATE: May 30, 2000

APPLICATION NUMBER: NDA 20-958

BETWEEN:

Name: Mr. George Latyszonek
Phone: (215) 273-7152
Representing: Merck Research Laboratories

AND

Name: Ms. Alice Kacuba; Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

BACKGROUND: NDA 20-958 for Pepcid/antacid combination tablets was found NA on February 18, 1999. On December 17, 2000, the firm submitted a complete response to our February 18, 1999 NA letter. In the resubmission, the firm included draft labeling. The May 25, 2000 submission, which was received today, includes revised draft labeling, which includes the addition of color and graphics. The cover letter mentions that only color and graphics have been added.

TODAY'S PHONE CALL:

I called Mr. Latyszonek to confirm that the only revisions to the labeling in the May 25, 2000 submission were the addition of colors and graphics and that the labeling text had not been revised from the last labeling that was submitted. He confirmed that the only revisions were the addition of colors and graphics.

The call was concluded.

/S/ 6.6.00

Alice Kacuba
Regulatory Health Project Manager

cc: Original NDA 20-958
HFD-180/Div. File
HFD-180/A.Kacuba

Drafted by: A.Kacuba/June 6, 2000
Final: AK/June 6, 2000
Filename: c:\mydocuments\20958\tcon-recent-labeling-submission.doc

TELECON

MEMORANDUM OF TELECON

DATE: February 2, 2000

APPLICATION NUMBER: NDA 20-958, Pepcid Complete Tablets

BETWEEN:

Name: George Latyszonek, Director, Regulatory Affairs
Abbie Gentry, Ph.D., Analytical Scientist
Andrew Kuzmission, Ph.D., Analytical Scientist
Phone: (215) 273-7152
Representing: Merck Research Laboratories.

AND

Name: Paul E. Levine, Jr., R.Ph., Regulatory Project Manager
Kati Johnson, Supervisory, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Division's response to the firm's request to use a new dissolution method.

BACKGROUND:

NDA 20-958 proposes to market (OTC) a combination famotidine/antacid (calcium carbonate 800 mg, and magnesium hydroxide 165 mg) tablet. The application was submitted February 20, 1998, and not approved on February 19, 1999, due to Clinical, and Chemistry, Manufacturing, and Controls (CMC) deficiencies. The CMC deficiencies included the requirement to develop a new dissolution method using Apparatus II.

On October 5, 1999, the firm submitted a request for guidance, proposing the use of Apparatus III in the dissolution testing of whole tablets, instead of Apparatus II.

Subsequent to this submission, on December 17, 1999, the firm submitted a complete response, to our Not Approvable letter. When this amendment was submitted, the agency had not yet responded to the firm's proposal to use Apparatus III. Consequently, the December 17, 1999, submission was thought to be incomplete since it did not appear to contain the revised dissolution study requested in the Not Approvable letter.

On 1/28/00, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) found the use of Apparatus III acceptable pending the firm's response to several requests.

THE CALL:

Mr. Latyszonek was informed that the use of Apparatus III in the dissolution testing of whole tablets is acceptable. However, the following information is required to determine whether the use of Apparatus III would be an interim or final regulatory method:

1. Provide dissolution data using whole tablet, 100 rpm, Apparatus II, 900 ml of acetate, at pH 4.5, without the SLS surfactant.

2. Provide dissolution data using Apparatus III with less than ———

3. Provide a rationale for using 900 ml of acetate medium with Apparatus III. Indicate whether data was acquired using volumes intermediate to 250 ml and 900 ml.

4. Clarify the results obtained using whole tablets using 0.1M HCl as the medium. These results are found in table 10, page 26, volume 1 of the December 17, 1999 submission. (Clarification refers to % dissolved - how much are famotidine and its degradents in the total % dissolved at each of the sampling time points).

Mr. Latyszonek stated that some of the requested information is in the December 17, 1999, submission and stated that he would send us a letter indicating the location of this information. Mr. Latyszonek also stated that the remaining requested information would be submitted in approximately one month.

During the conversation, it became clear that, although the December 17, 1999, submission did not contain the results from the new dissolution study recommended in our NA letter, and thus, was not considered a complete response, the firm included the results from a revised dissolution study (using Apparatus III). Therefore, the submission is considered a complete response. The FDAMA goal date for taking action on the amended application is June 20, 2000.

The call was concluded.

/S/

3/17/00

Paul E. Levine, Jr., R.Ph.
Regulatory Project Manager