CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020752

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-752

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
P.O. Box 4, BLA-20
West Point, PA 19486-0004

JUL 31 1997

Dear Dr. Kloss:

Please refer to your new drug application dated August 1, 1996, received August 2, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid RPD (famotidine) Rapidly Disintegrating Tablets.

We acknowledge receipt of your submissions dated August 13 and 16, September 12 and 13, October 4, 7, 11, 22, 25, and 29, and December 30, 1996; February 3 and 28, May 12, and June 13, 1997. The User Fee goal date for this application is August 2, 1997.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

a. Substances Expected to be Emitted.

b. Controls Exercised

c. Citation of and Statement of Compliance with Applicable Emission Requirements

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements.

This information should be provided for all sites of production, including the drug substance.

In addition, we have the following comments, recommendations, and requests for information that should also be addressed:

1. The proposed trade name "Pepcid RPD™" has been found acceptable.

   The dosage form name "Rapidly Disintegrating Tablets" is recommended for this formulation.

2. Your request for an exemption under 21 CFR 206.7(b)(1)(ii) for the requirement under 21 CFR 206.10 that the drug product be "clearly marked or imprinted with a code imprint that, in conjunction with the product's size, shape, and color, permits the unique identification of the drug product and the manufacturer or distributor of the product." is granted for a period of six months following approval of this application. Please commitment to submiting a supplement under 21 CFR 314.70(b) for marking the tablet to meet the requirements under 21 CFR 206.10 within six months of approval.

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 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

Sincerely yours,

7-31-97

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

cc:
Original NDA 20-752
HFD-180/Div. files
HFD-002/ORM
HFD-103/Office Director
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HFD-92/DDM-DIAB
HFD-180/M.Folkendt /S/ 7/31/97
HFD-180/K.Robie-Suh /S/ 7/31/97
HFD-180/A.Shaw 7/31/97
HFD-870/R.Pradhan /S/ 7/31/97

Drafted by: MF/July 25, 1997
Draft reviewed by: A.Shaw 7/30/97
E.Duffy 7/30/97
final: 7/31/97
filename: 20752707.NA

/S/ 7/31/97

NOT APPROVABLE (NA)

LABELING REVIEW

NDA: 20-752

MAY 26 1998

Drug: PEPCID RPD (famotidine) 20mg and 40mg

Sponsor: Merck Research Laboratories

APPEARS THIS WAY
ON ORIGINAL

Date of material reviewed: May 21, 1998

Receipt date: May 22, 1998

Reviewer: Bronwyn Collier, Associate Director for Regulatory Affairs, Office of Drug Evaluation III

Background: NDA 20-752 provides for a new dosage form, an oral tablet intended to dissolve on the tongue and then be swallowed without necessity for ingestion of water, for Pepcid (famotidine). A not approvable letter was issued July 31, 1997, for this application wherein the applicant was notified that the descriptive terms for the dosage form, "Wafer" and "RAPIDISC Wafer Formulation", were considered unacceptable by the Agency. Additional comments regarding dosage form nomenclature were relayed to the firm by telephone between Dr. Eric Duffy (FDA) and Dr. Michelle Kloss (MRL). The amendment reviewed was submitted in response to this call.

APPEARS THIS WAY
ON ORIGINAL

Review:

Photocopies of draft Immediate container and carton labels were submitted (Child Resistant Blisters, 20mg; carton, 40mg-30 count; carton, 40mg-100 count; Child Resistant blisters, 40mg; carton labels and Non-Child Resistant Blisters for Hospital Unit Dose Package; carton and Non-Child Resistant Blisters, 20mg complimentary package).

The submitted draft labeling was compared to that submitted December 4, 1997 (reviewed May 13, 1998).

APPEARS THIS WAY
ON ORIGINAL

1. The requested revision regarding changing the dosage form terminology from "rapidly disintegrating tablets" to "orally disintegrating tablets" was made to all submitted labeling.

APPEARS THIS WAY
ON ORIGINAL

2. None of the cartons or carton labels indicate the placement of the lot number or expiration date. In a telephone call on May 26, 1998, Dr. Michelle Kloss indicated that the lot number and expiration date will be imprinted by laser on all outer containers and/or container labels at the time of packaging.

Conclusions:

1. The submitted draft immediate container and carton labels are acceptable.

2. The applicant should be instructed to make the same dosage form terminology revision to the package insert. In addition, the revision to the statement in the CLINICAL PHARMACOLOGY section relating to peak plasma levels requested by the clinical reviewer remains outstanding (refer to labeling review dated 5/13/98).

/S/

CC:
Archival NDA 20-752
HFD-180/division file
HFD-180/M.Folkendt
K.Robie-Suh
A.Shaw
BC/5/26/98

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

LABELING REVIEW

NDA: 20-752

Drug: PEPCID RPD (famotidine) Orally Disintegrating Tablet, 20mg and 40mg

Sponsor: Merck Research Laboratories

Date of material reviewed: December 4, 1997

Receipt date: December 5, 1997

Reviewer: Bronwyn Collier, Associate Director for Regulatory Affairs, Office of Drug Evaluation III

Background: NDA 20-752 provides for a new dosage form, an oral tablet intended to dissolve on the tongue and then be swallowed without necessity for ingestion of water, for Pepcid (famotidine). A not approvable letter was issued July 31, 1997, for this application wherein the applicant was notified that the descriptive terms for the dosage form, "Wafer" and "RAPIDISC Wafer Formulation", were considered unacceptable by the Agency. The amendment reviewed, provides revised draft labeling and other information in response to the July 31, 1997, letter.

Review:

Package insert: The proposed package insert is common to PEPCID RPD, PEPCID Tablets (NDA 19-462), and PEPCID Oral Suspension (NDA 19-527). The draft insert was compared to the approved insert for PEPCID Tablets/PEPCID Oral Suspension (NDA 19-527/S-017).

1. Wording relating to description of the new dosage form as "wafer" were changed to be consistent with "rapidly disintegrating tablets" throughout the insert. The terminology "rapidly disintegrating tablets" was suggested in the July 31, 1997, letter. Further evaluation of the terminology by ONDC staff for this and other similar products, concluded in the recommendation to revise "rapidly disintegrating tablet" to "orally disintegrating tablet." This latter terminology is consistent with a USP proposal for this dosage form.

2. Information relating to the new dosage form was added to the DESCRIPTION, CLINICAL PHARMACOLOGY, PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections. These revisions were evaluated by the medical (refer to 3/28/97 review) and chemistry (refer to 7/16/97 and 5/11/98 reviews) reviewers. The content was found acceptable except for the statement added to the CLINICAL PHARMACOLOGY section relating to peak plasma levels. The medical reviewer recommends that this wording be changed to "After oral doses of either of the three formulations, peak plasma levels occur in 1-3 hours."

Immediate container and carton labels

1. Blister labels (40mg, 20mg, Complimentary package, Hospital Unit Dose packages) : Includes the same information as the blister labels for the approved tablet form except for a bar code. The term, "rapidly disintegrating tablet" should be revised to "orally disintegrating tablet"

2. Blister cartons: Information required by regulation is included except for placement of the lot number and expiration date. The dosage form should be revised to "orally disintegrating tablets."

Conclusions:

Package Insert: The proposed package insert conforms to labeling regulations. Changes requested concerning terminology for the dosage form were made as requested. However, the applicant should be notified of the additional change in dosage form terminology to "orally disintegrating tablet." In addition, the applicant should be instructed to revise the added text concerning peak plasma levels of the drug (CLINICAL PHARMACOLOGY section).

Immediate (blister) container and carton labels: The applicant should be notified of the additional change in dosage form terminology to "orally disintegrating tablet" and instructed to indicate the placement of the lot number and expiration date on the cartons.

Although not yet required, the applicant may revise the statement included on the immediate container and carton labels, "CAUTION: Federal (USA) law prohibits dispensing without prescription." to "Rx only" (refer to section 126 of the 1997 FDA Modernization Act).

CC:
Archival NDA 20-752
HFD-180/division file
HFD-180/M.Folkendt
K.Robie-Suh
A.Shaw
BC/5/13/98

/S/

5/13/98

REQUEST FOR TRADEMARK REVIEW

(715)

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	**Phone:** (301) 443-0487	
Date: October 28, 1996		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: Pepcid RPD	**NDA/ANDA#** NDA 20-752	
Established name, including dosage form: famotidine Rapidly Disintigrating Tablets (note: dosage form name still under consideration. See also the firms correspondence dated 10/22/96).		
Other trademarks by the same firm for companion products: For OTC use: Pepcid AC Acid Controller (tablets) for prescription use: Pepcid (tablets, oral suspension, injection, injection premixed)		
Indications for Use (may be a summary if proposed statement is lengthy): for the treatment of episodic heartburn and the prevention of meal induced heartburn.		
Initial Comments from the submitter (concerns, observations, etc.): -		

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 20-752; HFD-180/division file; HFD-180/M.Folkendt; HFD-180/A.Shaw

Rev. December 95

Consult #715 (HFD-180)

PEPCID RPD famotidine rapidly disintegrating tablets

The proprietary name PEPCID is already in use and was not considered by the Committee. The suffix "RPD" was evaluated and found not to conflict with any known medical abbreviations nor to be misleaading.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 1/7/97

CDER Labeling and Nomenclature Committee, Chair

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

NDA: 20-752
Famotidine
Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Famotidine	
2. Strengths	20 mg and 40 mg	
3. Trade Name	PEPCID	
4. Dosage form **Route of Administration**	Rapidly Dissolving Wafer Oral	
5. Applicant Firm Name	Merck Research Laboratories	
6. NDA Number	20-752	
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
	4,305,502	Expires: December 15, 1998
	4,371,516	Expires: January 31, 2000

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

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 three patents. U.S. Patent Nos. 4,283,408, 4,371,516 and 4,305,502 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, 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. 4,371,516, having an expiration date of January 31, 2000, and owned by John Wyeth & Brother Ltd., claims the drug product which is the subject of this application. The undersigned further declares that U.S. Patent No. 4,305,502, having an expiration date of December 15, 1998, and owned by John Wyeth & Brother Ltd., claims the drug product which is the subject of this application in that the dosage form is contained within the claimed package.

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.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-752

Trade Name: Pepcid RPD **Generic Name:** Famotidine Rapidly Disintigrating Tablets

Applicant Name: Merck Research Laboratories **HFD-180**

Approval Date: 5/28/98

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 /_X_/ NO /___/

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

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

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 6.

---

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 6 (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 # 19-462 (tablets) NDA # 20-249 (Injection Pre-Mixed)

NDA # 19-510 (Injection) NDA # 20-325 (Tablets for OTC use)

NDA # 19-527 (Oral Suspension)

APPEARS THIS WAY
ON ORIGINAL

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 6. IF "YES," GO TO PART III.

PART III <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

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

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

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 6:**

(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 /___/

Investigation #2 YES /_X_/ NO /___/

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 /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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 #____, Study # _____

Investigation #____, Study # _____

Investigation #____, Study # _____

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

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

Investigation #1

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

! _____

Investigation #2

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

! _____

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

Investigation #1

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

_____ | _____

_____ | _____

Investigation #2

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

_____ | _____

_____ | _____

(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
Regulatory Health Project Manager

6/2/98

Date

/S/

Signature of Division Director

6-2-98

Date

cc: Original NDA 20-752 HFD-180/Division File HFD-85/Mary Ann Holovac

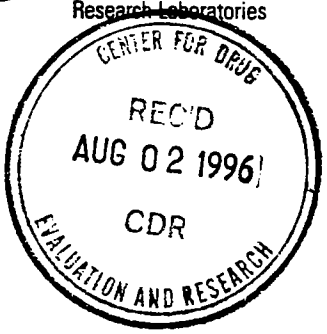
filename: 20752707.EXC

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
Fax 610 397 2516
Tel 610 397 2905
215 652 5000

August 1, 1996

MERCK
Research Laboratories



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, Maryland 20857

Dear Dr. Fredd:

Original New Drug Application: NDA 20-752
PEPCID RPD™ 20mg and 40mg Wafers (Famotidine)

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 PEPCID RPD™ (famotidine) Wafers.

APPEARS THIS WAY
ON ORIGINAL

PEPCID RPD™ is expected to be an effective alternate dosage form for the treatment of the approved indications because it has been demonstrated to be bioequivalent to famotidine tablets. The clinical efficacy of H_2-receptor antagonist therapy has been correlated with the extent and duration of the inhibition of acid secretion, and the two formulations exhibit similar bioavailability profiles at the 40mg strength. Therefore, it is expected that the 20 mg wafer and 20 mg tablet will also have comparable efficacy profiles, since the 20 mg wafer formulation is a direct submultiple of the 40 mg wafer formulation.

APPEARS THIS WAY
ON ORIGINAL

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 seventeen volumes, and four "review" copies as described in the Statement of Organization which is attached to this letter.

APPEARS THIS WAY
ON ORIGINAL

In accordance with the Prescription Drug User Fee Act of 1992, a check in the amount of was sent to the Food and Drug Administration

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 (Attention: Ms. Debra Pagano). 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 PEPCID RPD™ Wafers 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 Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Edwin L. Hemwall, Ph.D. (610/397-2306).

Sincerely,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Director, Regulatory Affairs

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

Federal Express #3

MEMORANDUM OF TELECON

DATE: May 19, 1998

APPLICATION NUMBER: NDA 20-752; Pepcid RPD (famotidine)

BETWEEN:

Name: Michelle W. Kloss, Ph.D.
Phone: 610-397-2905
Representing: Merck Research Laboratories

AND

/S/ 5/21/98

Name: Arthur B. Shaw, Ph.D. and Eric P. Duffy, Ph.D.
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: We called Dr. Kloss to convey the following questions (in *italics*) arising from my review

1. *Please provide the assay method and the data from the determination of aspartame*

This information will be provided in the first Annual Report. **ACCEPTABLE**

2. *Please revise the list of regulatory specifications to include the assay. A full description of the assay should be provided, including validation data. A description and specification for the used in the should be provided.*

This information will be provided via Fax, with hard copy to follow, except for the validation data, which may be provided in the first Annual Report. **ACCEPTABLE**

3. *Please specify the used in the famotidine assay. The g forces should be specified.*

4.

This information will be provided via Fax, with hard copy to follow. **ACCEPTABLE**

/S/ 5/21/98

Arthur B. Shaw, Ph.D.
Review Chemist

cc: Original NDA 20-752
HFD-180/Div. File
HFD-180/AShaw
HFD-180/Eduffy/5-21-98
HFD-181/Mfolkendt
ABS/dob **F/T 5-21-98**/c:\wordfiles\chem\N\20752805.AS1

TELECON

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-752

DEC - 2 1997

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
P.O. Box 4, BLA-20
West Point, PA 19486-0004

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Kloss:

We acknowledge receipt on November 28, 1997 of your November 26, 1997 amendment to your new drug application (NDA) for Pepcid RPD™ (famotidine) Rapidly Disintegrating Tablets.

This amendment contains additional Chemistry, Manufacturing, and Controls information submitted in response to our July 31, 1997 not approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is May 28, 1998.

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

APPEARS THIS WAY
ON ORIGINAL

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

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 20-752
HFD-180/Div. Files
HFD-180/CSO/M.Folkendt
DISTRICT OFFICE

/S/ 12/2/97

Drafted by: mf/December 2, 1997
Final: 12/2/97
filename: 20752712.ACK

ACKNOWLEDGEMENT (AC)

To Folkendt

NDA 20-752

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
BLA-20
West Point, PA 19486-0004

JAN - 7 1997

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Kloss:

Please refer to your pending August 1, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid RPD (famotidine) Rapidly Disintegrating Tablets, 20 and 40 mg.

We also refer to your amendments dated September 12, October 11, and December 30, 1996.

Your application states that the pharmacokinetic parameters for reference treatment were adjusted for the assay contents of the dosage forms (39.7 mg for and 40.0 mg for wafer). However, the data supporting this difference in the dosage form strengths was not presented in the application. To complete our review of the biopharmaceutical section of your submission, we request that you provide the data to support this dosage form strength correction and a bioequivalence analysis carried out without any dosage form correction.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-752
HFD-180/Div. Files
HFD-180/CSO/M.Folkendt
HFD-180/R.Pradhan

Drafted by: mf/January 6, 1997/20752701.1mf
Initialed by: R.Pradhan 1/6/97
S.Fredd 1/6/97
final: 1/6/97

/S/ 1/6/97

INFORMATION REQUEST (IR) /S/ 1/6/97

Folkendt

NDA 20-752

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
P.O. Box 4, BLA-20
West Point, PA 19486-0004

AUG 26 1996

Dear Dr. Kloss:

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 RPD™ (famotidine) Soluble Tablets, 20 and 40 mg

Therapeutic Classification: Standard

Date of Application: August 1, 1996

APPEARS THIS WAY
ON ORIGINAL

Date of Receipt: August 2, 1996

Our Reference Number: 20-752

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 October 1, 1996 in accordance with 21 CFR 314.101(a).

Should 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,

APPEARS THIS WAY
ON ORIGINAL

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

cc:
Original NDA 20-752
HFD-180/Div. Files
HFD-180/CSO/M.Folkendt
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

drafted: mf/August 23, 1996/20752608.1mf
Final: 8/23/96

ACKNOWLEDGEMENT (AC)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/~~PLA/PMA #~~ 20-752 ~~Supplement #~~ _____ ~~Circle one: SE1 SE2 SE3 SE4 SE5 SE6~~

HFD-180 Trade and generic names/dosage form: PEPCID RPD (famotidine) Orally Disintigrating Tablets Action: (AP) AE NA

Applicant Merck Research Laboratories Therapeutic Class 3/S

Indication(s) previously approved – NONE for this Dosage form –

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application Alternate Dosage form for Rx Pepcid (famotidine)

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? X Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) X Infants (1month-2yrs) X Children (2-12yrs) X Adolecents(12-16yrs)

APPEARS THIS WAY ON ORIGINAL

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- X c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - X (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **PEDIATRIC LABELING MAY NOT BE ADEQUATE.**

- ___ a. Pediatric studies are needed.
- ___ b. Pediatric studies may not be needed but a pediatric supplement is needed.

APPEARS THIS WAY ON ORIGINAL

___ 6. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ 5/28/98

Signature of Preparer and Title Date

cc: Orig NDA/~~PLA/PMA #~~ 20-752 /S/ 5-28-98
HFD-180/Div File
NDA/~~PLA~~ Action Package
HFD-006/ KRoberts (include labeling for all NME approvals;either draft or final)

(revised 9/15/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/~~PLA/PMA~~ # NDA 20-752 Supplement # -------- Circle one: ~~SE1 SE2 SE3 SE4 SE5~~ SE6

HFD-180 Trade and generic names/dosage form: Pepcid RPD (famotidine) ~~Rapidly Disintegrating Tablets~~ Action: AP AE (NA)

Applicant Merck Research Laboratories Therapeutic Class 3/S

Indication(s) previously approved Healing and Maintenance of healing of DU and GU Ulcers, ~~GERD, Erosive esophagitis, Hypersecretory conditions~~.
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application _____ (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

XX 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

****Currently being address in pending pediatric supplements.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ 7/31/97

Signature of ~~Preparer~~ and Title Date

cc: Orig NDA/~~PLA/PMA~~ #NDA 20-752
HFD-180/Div File
NDA/~~PLA~~ Action Package /S/ 7/31/97
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)
~~HFD-180/RPM~~

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL