CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020902

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

NDA 20-902

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

JUN 21 1999

Dear Mr. Latyszonek:

Please refer to your new drug application (NDA) dated September 30, 1997, received September 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for non-prescription Pepcid AC® (famotidine) Coated (gelatin coated, capsule shaped) Tablets.

We acknowledge receipt of your submissions dated December 18, 1998, January 26, February 2, and May 17, 1999. Your submission of December 18, 1998, constituted a complete response to our September 30, 1998, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

A. The following revisions must be made to conform with 21 CFR 201.66 of the new OTC labeling requirements final rule (64 FR 13254)(see also attached prototype label). If space is needed to accommodate the new standardized format and language, the product attributes located at the top of the back panel should be minimized or deleted.

1. The blister carton label appears to be in a modified format. Revise this label to be consistent with the standardized format described in § 201.66.

2. The sample pouch label must be revised to include the horizontal barlines and hairlines and format as described in § 201.66(d)(10)(v).

3. For the bottle carton, blister carton, and the dispensit, the bullets are gold (yellow) in color and do not appear to be 5-point type size. Thus, the bullets are not distinctive enough to provide a visual cue. To conform to § 201.66(d)(4), the bullets must be of 5-point type size, in a dark color, and be the same shape and color throughout the labeling such that these bullets are distinctive.

4. Revise the ***Warnings*** section as follows:

a. Revise the **Allergy alert** warnings statement to "**Allergy alert**: Do not use if you are allergic to famotidine or other acid reducers" (i.e., remove the proprietary name "Pepcid AC" from this statement).

b. Revise the "**Do not use**" warnings statement to:

Do not use
- if you have trouble swallowing
- with other acid reducers

c. Revise the title, text, and format of the proposed ***Warnings*** subsection that begin with "**Ask a doctor before use if you have**" to:

Stop use and ask a doctor if
- stomach pain continues
- you need to take this product for more than 14 days

d. Delete the proposed ***Warnings*** subsection "**When using this product** do not take the maximum daily dosage (2 gelcaps) for more than 2 weeks continuously except under the advice and supervision of a doctor." This information is now incorporated in the **"Stop use and ask a doctor if"** subsection of the ***Warnings*** as the second bullet statement "you need to take this product for more than 14 days," and in the ***Directions*** section as a bullet statement "do not use more than 2 tablets in 24 hours."

5. Revise the format and text of the ***Directions*** section to:

Directions
- adults and children 12 years and over:
  - to **relieve** symptoms, swallow 1 gelcap with glass of water
  - to **prevent** symptoms, swallow 1 gelcap with a glass of water at any time from **15 to 60 minutes before** eating food or drinking beverages that cause heartburn
  - do not use more than 2 tablets in 24 hours
- children under 12 years: ask a doctor

B. Regarding the package insert, modification of the headings and format should be made to be consistent with the labeling format from the OTC labeling final rule. Also, for the package insert, under "How to use PEPCID AC Gelcaps," revise the phrase "Use PEPCID AC to relieve or prevent these symptoms:..." to "Use Pepcid AC Gelcaps to relieve or prevent heartburn due to acid indigestion and sour stomach."

C. Identify the location where the expiration date and the lot number are printed for the 50, 54, and 70 tablet bottles.

D. The text in the corner flag on the principal display panel of the blister card cartons "NEW!" is misleading because it can imply that this is a new product, rather than a new dosage form of an existing product. Revise the text in this flag to "NEW! GELCAPS." In addition, please commit to deleting this flag after six months of marketing.

E. Concerning the yellow flag on the principal display panel of the bottle cartons, clarify the text in this flag as to whether the package size is new or what makes the bottle more convenient than other bottles. In addition, please commit to deleting this flag after six months of marketing.

F. At the top of the back panel of the carton label for the bottles, blister cards, and the dispensit cartons, the word "Fast" in the statement "PEPCID AC is Now Available in a Fast and Easy-to-Swallow Gelcap" is misleading and must be deleted. In addition, please commit to deleting this revised statement after six months of marketing.

G. Revise the storage statement under the "***Other information***" section from "store between 25 - 30°C (77 - 86°F)" to "store at 25 - 30°C (77 - 86°F)."

H. For consistency with the indication under the ***Uses*** section, we request that you revise the following:

1. All instances of the phrase "Relieves & Prevents Heartburn and Acid Indigestion" to "Relieves & Prevents Heartburn due to Acid Indigestion"

2. At the top of the back panel of the cartons and sample pouch dispensit, revise the bulleted phrases:

   a. "1 gelcap relieves heartburn and acid indigestion" to "1 gelcap relieves heartburn due to acid indigestion."

   b. "PEPCID AC prevents heartburn and acid indigestion..." to "PEPCID AC prevents heartburn due to acid indigestion..."

I. To better conform to § 201.61 stating that the statement of identity must in direct conjunction with the most prominent display of the proprietary name and must be in bold face type on the principal display panel in a size related to the most prominent printed matter, we request that the type size of the statement of identity be increased to a size related to the type size of the proprietary name "Pepcid AC."

J. We request that you consider repeating the statement "read the directions and warnings before use" outside the ***Drug Facts*** labeling section in a conspicuous location.

K. For the immediate bottle label, the sponsor should consider following the provisions in § 201.66(d)(10)(i) through (d)(10)(v) for the modified format. For consumer readability, we suggest using a 6-point type size.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit four copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products, one to the Division of Over-the-Counter Drug Products, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

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

If you have any questions, contact Michael Folkendt, Project Manager, at (301) 827-1602.

Sincerely,

/S/ 6-21-99

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

Attachment 1: Suggested Drug Facts Label for Famotidine Gelatine Coated Tablets

DRUG FACTS

Active ingredient (in each gelcap) — **Purpose**

Famotidine 10 mg ..... Acid reducer

Uses

- relieves heartburn associated with acid indigestion and sour stomach
- prevents heartburn associated with acid indigestion and sour stomach brought on by eating or drinking certain food and beverages

Warnings

Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use

- if you have trouble swallowing
- with other acid reducers

Stop use and ask a doctor if

- stomach pain continues
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults and children 12 years and over:
  - to relieve symptoms, swallow 1 gelcap with a glass of water
  - to prevent symptoms, swallow 1 gelcap with a glass of water at any time from **15 to 60 minutes** before eating food or drinking beverages that cause heartburn
  - do not take more than 2 tablets in 24 hours
- Children under 12 years: ask a doctor

Other information

- keep the carton and package insert. They contain important information.
- store at 25 - 30°C (77 - 86°F)
- protect from moisture

Inactive ingredients (list in alphabetical order.)

Questions or comments? call toll-free 1-8XX-XXX-XXXX

In addition, the following may be included on the carton back panel under the other information section or in the package insert:

Tips for managing heartburn

- do not lie flat or bend over soon after eating
- do not eat late at night, or just before bedtime
- certain foods or drinks are more likely to cause heartburn, such as rich, spicy, fatty, and fried foods, chocolate, caffeine, alcohol, even some fruits and vegetables
- eat slowly and do not eat big meals
- if you are overweight, lose weight
- if you smoke, quit smoking
- raise the head of your bed
- wear loose fitting clothing around your stomach

CSO/Folkendt

NDA 20-902

SEP 30 1998

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

Dear Mr. Latyszonek:

Please refer to your new drug application (NDA) dated September 30, 1997, received September 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for nonprescription Pepcid AC® Gelcap (famotidine) Coated Tablets.

We acknowledge receipt of your submissions dated October 9 and December 10, 1997, May 12, June 19 and 21, 1998. The user fee goal date for this application is September 30, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Regarding the production operations:

   a. It is unclear what the differences are between the actual present manufacturing practice and the "Proposed Commercial Production" (Volume 1.2, page 03-041). Provide a chart with the differences in dosage form manufacturing between the actual present manufacturing practice and the "Proposed Commercial Production" and scientifically justify the differences with respect to the production of a consistent drug product equivalent to the clinical trial batches.

   b. As a part of the "Proposed Commercial Production" scheme, the following must be provided:

      i. The dosage [redacted] holding time and storage conditions from the date of manufacture to the date that the [redacted] enter the [redacted]

      ii. The finished dosage form holding time and storage conditions from the date of manufacture to the date that the dosage form is placed in the finished packaging.

      iii. The method and an example of the calculation for drug product expiry dating.

      iv. The details under "3.3.5 Manufacturing Process, In-Process Control Guides, and Packaging Procedure" for the following: