CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-958

JUN 20 2000

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

Dear Mr. Latyszonek:

Please refer to your new drug application (NDA) dated February 20, 1998, received February 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid® Complete [famotidine 10 mg/antacid (calcium carbonate 800 mg, and magnesium hydroxide 165 mg) Chewable Tablets.

We acknowledge receipt of your submissions dated November 19 and December 11, 1998, January 20, January 22, February 24, March 18, October 5, December 7, December 17, 1999, January 18, February 22, March 10, May 16, May 25, and June 1, 2000. Your submission of December 17, 1999 constituted a complete response to our February 19, 1999 action letter.

We also refer to your submission dated June 9, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this 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 address the following:

Clinical/Statistical

The primary analyses for onset and duration were based on logistic regression on ordered categorical data (grouping time points), including investigator (33 binary terms) and severity (linear effect) with a GEE model (constant correlation between episodes and patients) to incorporate multiple episodes per patient. This is an extremely complex model, with many assumptions and interlocking parts. The study report did not adequately address the validity of these and did not assess the robustness of the model compared to similar models or to other analytical methods. Accordingly, we do not consider that the efficacy of the combination product has been demonstrated. Please provide further analyses verifying the assumptions of the GEE model or demonstrating the robustness of the results to deviations from the assumptions.

Chemistry

An adequate response to our Chemistry Discipline Review letter dated May 31, 2000, requesting additional chemistry information.

Labeling

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling and must be formatted consistent with the requirements of 21 CFR 201.66. Please note that the labeling may be further revised based on your response to our request for additional clinical/statistical information.

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

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit two 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 and one copy to the Division of Over-the-Counter Drug Products.

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 Alice Kacuba, R.N., MSN, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

/S/

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

/S/

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

Enclosure

cc:
Archival NDA 20-958
HFD-180/Div. Files
HFD-180/A.Kacuba
HFD-180/P.Levine
HFD-180/L.Talarico
HFD-180/S.Aurecchia
HFD-180/H.Gallo-Torres
HFD-180/S.Kress
HFD-180/L.Zhou
HFD-180/M.Adams
HFD-870/S.Doddapaneni
HFD-715/T.Permutt
HFD-560/C.Ganley
HFD-560/L.Katz
HFD-560/A.Segal
HFD-560/D.Keravich
HFD-560/H.Cothran
HFD-560/G.Chang
HFD-002/ORM
HFD-103/ADRA
HFD-40/DDMAC (with labeling)
HFD-560/OTC/ (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: A.Kacuba/May 26, 2000
Initialed by: L.Zhou/June 6, 2000
Initialed by: M.Adams/June 6, 2000
Initialed by: S.Aurecchia/June 18, 2000
Initialed by: K.Johnson/June 19, 2000
Initialed by: L.Katz/June 19, 2000 6/19/00
Initialed by: C.Ganley/June 19, 2000
Initialed by: R.Cook/June 19, 2000
Final: DK/June 19, 2000
Filename: c:\mydocuments\20958AE-letter.doc

APPROVABLE (AE)