DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

June 16, 1998

TRANSMITTED BY FACSIMILE

Mr. David Anstice
President, US Human Health Division
Merck & Co., Inc.
P.O. Box 4, WP39-401
West Point, PA 19486

Re: NDA No. 19-527 Pepcid (famotidine) Oral Suspension
NDA No. 20-249 Pepcid (famotidine) Injection
NDA No. 16-059 Indocin (indomethacin)
NDA No. 20-386 Cozaar (losartan potassium) Tablets
NDA No. 20-387 Hyzaar (losartan potassium-hydrochlorothiazide) Tablets
NDA No. 50-587 Primaxin I.V. (imipenem and cilastatin for injection)

WARNING LETTER

Dear Mr. Anstice:

This Warning Letter addresses Merck & Co., Inc.'s (Merck) dissemination of select promotional materials for its products Pepcid, Indocin, Cozaar, Hyzaar, and Primaxin. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these materials as part of its monitoring and surveillance program. DDMAC has concluded that the Merck promotional materials, cited below, are misleading and lacking in fair balance in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a), 331(a), and 321(n), and applicable regulations concerning labeling for prescription drugs. Despite numerous interactions between DDMAC and Merck, DDMAC has reason to believe that Merck has engaged in, and continues to engage in the dissemination of promotional materials that lack fair balance and thus, violate the Act. By its dissemination of these misleading promotional materials, Merck is misbranding Pepcid, Indocin, Cozaar, Hyzaar, and Primaxin.

Background

Issues concerning reasonably comparable presentations of fair balance information are not new issues relating to Merck's promotional materials. To the contrary, such issues

have been raised in regard to promotional materials for a variety of products and suggest a corporate policy toward minimizing the presentation of such disclosures. Furthermore, DDMAC has expressed its concerns about Merck's failure to adequately present such information on numerous occasions. For example, untitled letters dated January 26, 1998, concerning Zocor; October 20, 1997, concerning Cozaar and Hyzaar; and August 6, 1997, concerning Fosamax all contained descriptions of materials that had one common violation. That violation was Merck's failure to present information relating to contraindications, warnings, and other risk information with a prominence and readability reasonably comparable to the presentation of information relating to effectiveness of the drug. In considering the presentation of such information, all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and other techniques likely to achieve emphasis are taken into account. Merck's promotional materials for a variety of products repeatedly fail to present the risk information in a reasonably comparable manner.

In prior correspondence from Merck responsive to DDMAC's letters, Merck agreed to discontinue or revise its materials. For example, in a letter dated February 10, 1998, although Merck did not agree with DDMAC's objections, it stated that it had discontinued use of promotional materials for Zocor that contained the issues of prominence of risk information. In Merck's response dated November 3, 1997, it agreed to present information about the risks associated with the use of Cozaar and Hyzaar in a manner reasonably comparable to the claims concerning efficacy. In its August 20, 1997, response to DDMAC's letter concerning Fosamax, Merck agreed to discontinue the cited promotional materials.

Current Violations

Notwithstanding these actions and responses, Merck is still not in compliance with the requirement for reasonably comparable presentation of risk information in its promotional materials and repeatedly continues to disseminate violative promotional materials. These violative materials include the following recent examples:

- Merck submitted, under cover of Form FDA 2253, two versions of detail aid mug wrappers for Pepcid identified as 98073(1)-05-PEP and 983074(1)-05-PEP. Both of these wrappers contain numerous product claims. However, neither of these promotional items contain a reasonably comparable presentation of information relating to the side effects associated with the use of the drug.

- Merck submitted, under cover of Form FDA 2253, a promotional brochure for Pepcid identified as 983075(1)-05-PEP. In this brochure Merck presents the most prevalent adverse events associated with the use of Pepcid on the bottom of the front cover of the brochure and minimizes the impact of this information by

presenting it in very small type size and to the left of the large, colorful product name and logo. Moreover, Merck separates the presentation of the most common adverse events associated with the use of Pepcid from the information in the brochure it discloses under the heading "tolerability." That presentation contains claims that certain adverse effects were not identified with Pepcid and were presented in a clear and prominent manner. Thus, Merck's presentation of information to healthcare practitioners about the risks associated with the use of Pepcid is misleading.

- Merck submitted, under cover of Form FDA 2253, a photograph of a promotional poster for Indocin, identified as 976183-11-COX. We recognize that this 6" x 9" photograph is a reduction of the size of the actual poster. However, information about the contraindication for the product was presented in faint type, only 1 mm in height. This presentation is compared to the large, bolded, and outlined presentation of statements concerning the benefits of the product. Thus, this poster fails to provide the contraindication to the use of the drug in a reasonably comparable manner to the presentation of information relating to benefits.

- Merck submitted, under cover of Form FDA 2253, a promotional brochure identified as 981322-05-COZ, to promote both Cozaar and Hyzaar. This brochure is 20 pages long, not including both sides of the cover pages. On page 5, Merck presents bulleted information that the adverse events of Cozaar were similar to placebo, and on pages 14-17, Merck presents data on some selected, positively presented adverse events under a tab entitled "Tolerability/Experience." It is not until the sterile presentation[1] on page 20 of the brochure that Merck discloses, under the heading "Selected Prescribing Information," information about the consequences that may occur from the use of Cozaar or Hyzaar. It is not until page 20 that Merck discloses the boxed warning concerning the use of these drugs in the second and third trimesters of pregnancy. It is not until page 20 that Merck discloses fair balance information concerning the risks associated with the use of these products such as hypersensitivity to sulfa (Hyzaar), reports of angioedema, or changes in renal function. In a prominent bulleted disclosure on page 11, Merck discloses that "[T]he overall response to Hyzaar was similar for black and nonblack patients." However, it is not until page 20 that Merck discloses that Cozaar had an effect on blood pressure that was "notably less in blacks patients than in nonblack patients." Thus, this brochure fails to present the risk information associated with the use of Cozaar and Hyzaar in a reasonably comparable manner to Merck's promotional messages.

---

1 Sterile describes the manner of presentation compared to the bold, colorful, bulleted presentations of promotional messages throughout the brochure.

- Merck submitted, under cover of Form FDA 2253, a promotional brochure for Primaxin I.V. identified as 981195-05-PRI. This brochure is five pages long not counting both sides of the front and rear covers, is replete with colorful headers and graphs, and utilizes bolding, italics and bullets to highlight and emphasize Merck's promotional messages. However, the important risk information, including information about the incidence of "pseudomembraneous colitis" and "serious and occasionally fatal hypersensitivity (anaphylactic) reactions," are not disclosed except for a statement below the footnotes on the bottom of pages 2 and 4 respectively. These presentations of risk information are not reasonably comparable to Merck's claims of effectiveness of the product.

Conclusions and Requested Actions

DDMAC is seriously concerned that the dissemination of the above-listed promotional materials demonstrate a continuing pattern and practice of widespread corporate behavior to avoid compliance with the regulations concerning the disclosure of risk information. Despite Merck's previous responses to DDMAC's letters, that such information will be appropriately presented in new materials, such assurances have not been followed by actions to bring Merck's promotional materials into compliance with the Act and regulations. Consequently, we request that Merck provide a detailed response to these issues on or before July 1, 1998. This response should contain an action plan that includes:

1. immediately ceasing the dissemination of all advertising and labeling materials for these products that fail to clearly and prominently disclose balancing information in a manner reasonably comparable to the benefit claims;

2. reviewing its promotional materials for **all of its products** and to discontinue or revise any materials with the same or similar violations;

3. a written statement of Merck's intent to comply with "1" and "2" above; and

4. a proposal to disseminate accurate and complete information to the audiences that received Merck's misleading messages.

If Merck has any questions or comments, please contact Thomas Abrams, Dr. Tracy Acker, or Norman A. Drezin, Esq., by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD, 20857. DDMAC reminds Merck that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID #6637.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

/S/

Minnie Baylor-Henry, R.Ph., J.D.
Director
Division of Drug Marketing,
Advertising and Communications