DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG - 6 1997

TRANSMITTED VIA FACSIMILE

Ellen R. Westrick
Senior Director, Office of Medical/Legal
Merck & Co., Inc.
P.O. Box 4, WP37B-113
West Point, Pennsylvania 19486

RE: **NDA 20-560**
Fosamax (alendronate sodium tablets)
MACMIS ID #5691

Dear Ms. Westrick:

Reference is made to Merck & Co. Inc.'s (Merck) March 6, 1997, May 16, 1997, May 30, 1997, and July 2, 1997, FDA form 2253 submissions for Fosamax. These materials consist of the following:

- 972745 Brochure submitted March 6, 1997
- 972500 Brochure submitted March 6, 1997

- 971026 Brochure submitted May 16, 1997
- 972648 Brochure submitted May 16, 1997

- 972269(5)(005) Journal Ad submitted May 30, 1997

- 971027 Reprint Holder submitted July 2, 1997
- 9773776W Slide Presentation submitted July 2, 1997

The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these materials and has determined that they are misleading in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations for the following reasons:

Risk Information

The slide presentation (9773776W), reprint holder (971027), brochure (972500), and journal ad (972269(5)(005) are misleading because they fail to present important risk information for Fosamax and thus lack fair balance, as discussed in DDMAC's

April 14, 1997, notice of violation (NOV) letter and May 20, 1997, letter of comments. In these letters, DDMAC stated that Merck fails to present important risk information for Fosamax including the warning regarding serious esophageal adverse experiences and the dosing and administration restrictions.

The brochure (972500) fails to present contraindications and warnings for Fosamax. The reprint holder, slide presentation, and journal ad fail to present the warning regarding reports of serious esophageal adverse experiences reported in patients receiving Fosamax and the need to discontinue therapy if symptoms develop. For example, the presentation of the statement, "Esophagitis ulcers and erosions have been reported; consult prescribing information for complete listing of adverse experiences," in small type at the end of the list of adverse experiences in the slide kit is not adequate to communicate this important warning.

The brochures (972648, 971026, and 972745) and journal ad lack fair balance because the presentation of risk information is not reasonably comparable to the efficacy information, as discussed in DDMAC's April 14, 1997, notice of violation (NOV) letter, May 20, 1997, and May 30, 1997, letters of comments. In these letters, DDMAC stated that the risk information was presented in a manner that lacks prominence and is not reasonably comparable to the presentation of the efficacy information.

Merck continues to present the risk information in a manner that is not reasonably comparable to the efficacy information. The brochure (972745) presents the contraindications and warning information in small footnotes. The brochures (971026, 972648) present the esophageal warning information in small type at the bottom of the page. Further, the presentation of the warning regarding the dosing restriction in block text at the bottom of the page lacks prominence in relation to the presentation of efficacy information. The contraindications in the brochures (971026, 972648) and journal ad are also presented in a nonprominent manner at the bottom of the page overlaying the picture of the woman.

Efficacy Information

The presentation of efficacy information in the reprint holder (971027) is misleading because the chart discussing the effect of Fosamax on fracture incidence states in bold type that Fosamax reduced the incidence of "any clinical (i.e. painful) fracture"

by 28%. However, there was no significant difference in the proportion of women with non-vertebral fractures in this study, as discussed in DDMAC's April 23, 1997, letter of comments. In that letter, DDMAC stated that it would be misleading to include the statement, "The ability of Fosamax to prevent fractures at all major sites, including the hip, has been demonstrated in the Vertebral Fracture are of the Fracture Intervention Trial (FIT)" because there was no significant difference in the proportion of women with non-vertebral fractures in this study. In the reprint holder, the inclusion of the small footnote statement "Non-osteoporotic fractures were not significantly reduced," would not be adequate to correct this misleading message.

Additionally, the slide presentation fails to present information about the risk factors often associated with the development of postmenopausal osteoporosis, as discussed in the indications section of the approved product labeling.

In order to address these violations, DDMAC requests that Merck immediately discontinue the dissemination and use of the violative pieces noted in this letter and any other promotional materials that contain similar themes. DDMAC requests that Merck submit a written response to this letter no later than August 20, 1997. This response should include the following:

- A list of all materials that have been discontinued;
- Merck's plan to comply with DDMAC's request;

If Merck has further comments or issues, please contact me at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

In all future correspondence related to this matter, please refer to MACMIS ID #5691 and the NDA number.

Sincerely,

Anne M. Reb, MS, NP
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications