DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JAN 22 1999

William J. Kennedy, Ph.D.
Vice President, Drug Regulatory Affairs
Zeneca Pharmaceuticals
1800 Concord Pike
Wilmington, De 19850-5437

RE: NDA 17-970/S-040
Nolvadex (tamoxifen citrate)
MACMIS ID# 7432

Dear Dr. Kennedy:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional labeling and advertising materials for Nolvadex (tamoxifen citrate) disseminated by Zeneca Pharmaceuticals (Zeneca) that violate the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Reference is made to a direct-to-consumer (DTC) Journal Advertisement (NL 1203) that appeared in the December/January 1999 issue of *Mamm* magazine. Reference is also made to a Fisher reprint carrier (NL 1210), submitted under cover of Form FDA 2253 on December 24, 1998. DDMAC has reviewed these materials and has determined that they contain promotional claims that are false or misleading and lacking in fair balance. DDMAC requests that the use of the above referenced materials and those containing similar promotional claims cease immediately.

Journal Advertisement

The advertisement in its entirety makes a representation about the product and its intended population (making it a product ad rather than a reminder ad). The pictorial presentation only of women makes a representation concerning the intended patient population of Nolvadex. Therefore, DDMAC considers this advertisement to be a full product ad and in violation of the Act for the following reasons:

- it fails to provide adequate information regarding Nolvadex's approved indication and usage,

- it fails to include any risk information, and
- it fails to present a brief summary of information related to side effects, contraindications, and effectiveness.

Failure to Comply with 314.81 (b)(3)(i)

Since the journal advertisement was not submitted on Form FDA 2253 at the time of initial dissemination, Zeneca has violated the postmarketing reporting requirements of the Act.[1] Moreover, reference is made to Zeneca's letters dated December 9, 1998, and January 7, 1999, wherein Zeneca did not reference the aforementioned journal advertisement as being continued or discontinued.

Fisher "Reprint Carrier" (Brochure)

The Fisher brochure, containing the reprint Fisher, B. MD et al., Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study, J NCI, 1998; 90: 1371-88, is, in fact, a promotional detail aid or brochure. This brochure contains promotional claims that are false or misleading and lacking in fair balance. DDMAC objects to the use of this material for the following reasons:

- Zeneca's failure to discuss the Gail Model Risk Assessment Tool in the brochure undermines the importance of an accurate risk assessment. This material omission is dangerously misleading because Zeneca fails to adequately define women at high risk.

- Promotional materials are lacking in fair balance, or otherwise misleading if they fail to present information relating to the contraindications, warnings, precautions, and side effects associated with the use of the drug in a manner reasonably comparable to the presentation of efficacy information. The risk information contained in the reprint carrier lacks the prominence, readability, scope, and depth that Zeneca dedicated to the presentation of efficacy information.

- Zeneca's use of the word "uncommon" to modify endometrial cancer is misleading because it minimizes the significance of this serious risk. This description does not adequately communicate the fact that healthy women had a 2½ times increased risk of getting endometrial cancer on Nolvadex as compared to placebo.

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[1] 21 CFR 314.81 (b) (3) (i)

- The brochure fails to provide sufficient emphasis for the information relating to side effects or contraindications, when such information is distorted because of repetition or other emphasis on claims for effectiveness. The presentation of safety information was selectively intertwined with the benefits so as to minimize the risks associated with therapy. For example, the perceived benefits of Nolvadex therapy (fewer fracture events and no effect on ischemic heart disease) were presented with proximity to risk information so as to minimize the adverse events associated with therapy.

- Zeneca's use of the chart listing "criteria for evaluating high risk" is misleading because it promotes the use of Nolvadex in an unapproved patient population. Although one of the BCPT criteria for participation in the study was women over 60 years old, such women are not included in the indicated population unless they also have a 5-year predicted risk of breast cancer >1.67%, as calculated by the Gail Model.

- Misleading efficacy data contained in the brochure that is inconsistent with the approved product labeling (PI) include:
  - 49% reduction in the incidence of breast cancer vs. 44% (PI)
  - 4.6 years median follow-up time vs. 4.2 (PI)
  - 36.8% of women had follow-up > 5 years vs. 25% (PI)

- Material information that is missing from the reprint carrier but contained in the approved product labeling includes:
  - Nolvadex does not normalize the risk of breast cancer in high risk women
  - In the BCPT study, Nolvadex had no impact on survival
  - Nolvadex may not be appropriate for all women at high risk

- The claims relative to fewer fracture events are misleading because they are not supported by statistically significant evidence.

- While prevention of breast cancer in women at high risk may have been the hypothesis tested in the trial (and thus influenced the name of the study), the results, in fact, did not demonstrate that Nolvadex prevents breast cancer. Rather, the data showed that Nolvadex may reduce the incidence of breast cancer in women at high risk. Hence, Zeneca was informed, in previous discussions with the Agency, that use of the term "prevention" would be false and/or misleading. DDMAC has no objection to the cover of the brochure that accurately presents the title of the study. However, page 2 of the brochure repeatedly refers to the "Breast Cancer Prevention Trial." This

presentation misleadingly promotes Nolvadex for "prevention."

Zeneca should immediately cease using the journal advertisement, Fisher reprint carrier, and all other promotional materials for Nolvadex that contain the same or similar claims or presentations. Zeneca should submit a written response to DDMAC, on or before February 5, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, Zeneca should include a list of all promotional materials that were discontinued, and the discontinuation date.

Zeneca should direct its response to the undersigned by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-40; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Zeneca that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS#7432 and NDA 17-970/S-040.

Sincerely,

Michael A. Misocky ~~R.Ph.~~, J.D
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications.