DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Ms. Christine (Duffy) Smith
Director, Promotional Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

RE: NDA # 17-970
Nolvadex® (tamoxifen citrate) Tablets
MACMIS # 10205

Dear Ms. Smith:

This letter notifies AstraZeneca Pharmaceuticals LP (Zeneca) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional activities that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, Zeneca promoted misleading efficacy information about Nolvadex and minimized the risks associated with its use in a direct-to-consumer (DTC) magazine advertisement in the September 2001, issue of *InTouch*.[1]

Misleading Efficacy Information

The DTC advertisement promotes use of Nolvadex as adjuvant therapy (i.e., to be used after other interventions such as surgery and/or radiation therapy) for women with breast cancer. However, the DTC advertisement is misleading because it does not provide adequate context for efficacy information about Nolvadex, thereby implying greater efficacy than demonstrated by substantial evidence. For example, Zeneca presents the statement "Major findings from the Overview prove that five years of Nolvadex reduces the incidence of new cancers in the opposite breast by 47%." Promoting a 47% relative risk reduction in the incidence of new cancers in the opposite (i.e., contralateral) breast without additional context is misleading because it overstates the efficacy of Nolvadex therapy in reducing the occurrence of contralateral breast cancer in patients receiving adjuvant Nolvadex therapy for breast cancer. For patients to understand the 47% relative risk reduction, additional context should have been supplied. For example, the DTC advertisement could have disclosed the absolute number of cases of contralateral breast cancer annually/1,000 women who took Nolvadex

[1] "I reduced my chances for a recurrence of breast cancer significantly" (NL1298).

versus those who took placebo. Zeneca does not provide this, or similar, context in the advertisement.

Furthermore, Zeneca also states that "In the Overview, one and two years of Nolvadex reduced breast cancer recurrence by 18% and 25%, respectively; five years reduced breast cancer recurrence by 42%. For women who are estrogen receptor (ER) positive status or estrogen receptor (ER) unknown, five years reduced their recurrence by 47%. In women who are ER negative, 5 years of Nolvadex reduced recurrence by 6% with no survival benefit." Again, such a relative risk presentation overstates the efficacy of Nolvadex because it lacks sufficient context for patients to accurately interpret the efficacy information.

Minimization of Risk Information

This advertisement is misleading because the listing of common adverse effects for Nolvadex first in the fair balance discussion minimizes the more serious risk information about the risk of developing uterine cancer or blood clots in the legs, which is included in the warnings section of the approved product labeling (PI).

Furthermore, this advertisement is also misleading because it minimizes the incidences of the common adverse effects in women who received Nolvadex as adjuvant therapy for breast cancer. As stated in the PI:

> *"[In the NSABP B-14 study,] the incidence of hot flashes (64% vs. 48%), vaginal discharge (30% vs. 15%), and irregular menses (25% vs. 19%) were higher with Nolvadex compared with placebo. All other adverse effects occurred with similar frequency in the 2 treatment groups, with the exception of thrombotic events; a higher incidence was seen in Nolvadex - treated patients (through 5 years, 1.7% vs. 0.4%). Two of the patients treated with Nolvadex who had thrombotic events died."*
>
> *"[In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial,] compared to placebo, Nolvadex showed a significantly higher incidence of hot flashes (19% vs. 8% for placebo). The incidence of all other adverse reactions was similar in the 2 treatment groups with the exception of thrombocytopenia where the incidence for Nolvadex was 10% vs. 3% for placebo, an observation of borderline statistical significance."*
>
> *"In the Toronto study, hot flashes were observed in 29% of patients for NOLVADEX vs. 1% in the untreated group. In the NATO trial, hot flashes and vaginal bleeding were reported in 2.8% and 2.0% of women, respectively, for NOLVADEX vs. 0.2% for each in the untreated group.*

Zeneca undermines the significance of these adverse events in its advertisement by stating "In general, most side effects were hormonal in nature: hot flashes, vaginal discharge, and irregular periods. Most were considered relatively mild, and few women - 5% - discontinued their therapy." Hot flashes, vaginal discharge, and irregular periods occurred in much higher incidences in patients receiving Nolvadex as compared to those receiving placebo.

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

In addition, this advertisement was not submitted on Form FDA 2253 at the time of initial dissemination, in violation of the post-marketing reporting requirements of the Act.

Requested Actions

Zeneca should immediately cease distribution of this and other similar promotional materials for Nolvadex that contain the same or similar claims or presentations. Zeneca should submit a written response to DDMAC on or before January 3, 2002, describing its intent and plans to comply with the above request. In its letter to DDMAC, Zeneca should include the date on which this and other similarly violative materials were discontinued.

Zeneca should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID # 10205 in addition to the NDA number. DDMAC reminds Zeneca that only written communications are considered official.

Sincerely,

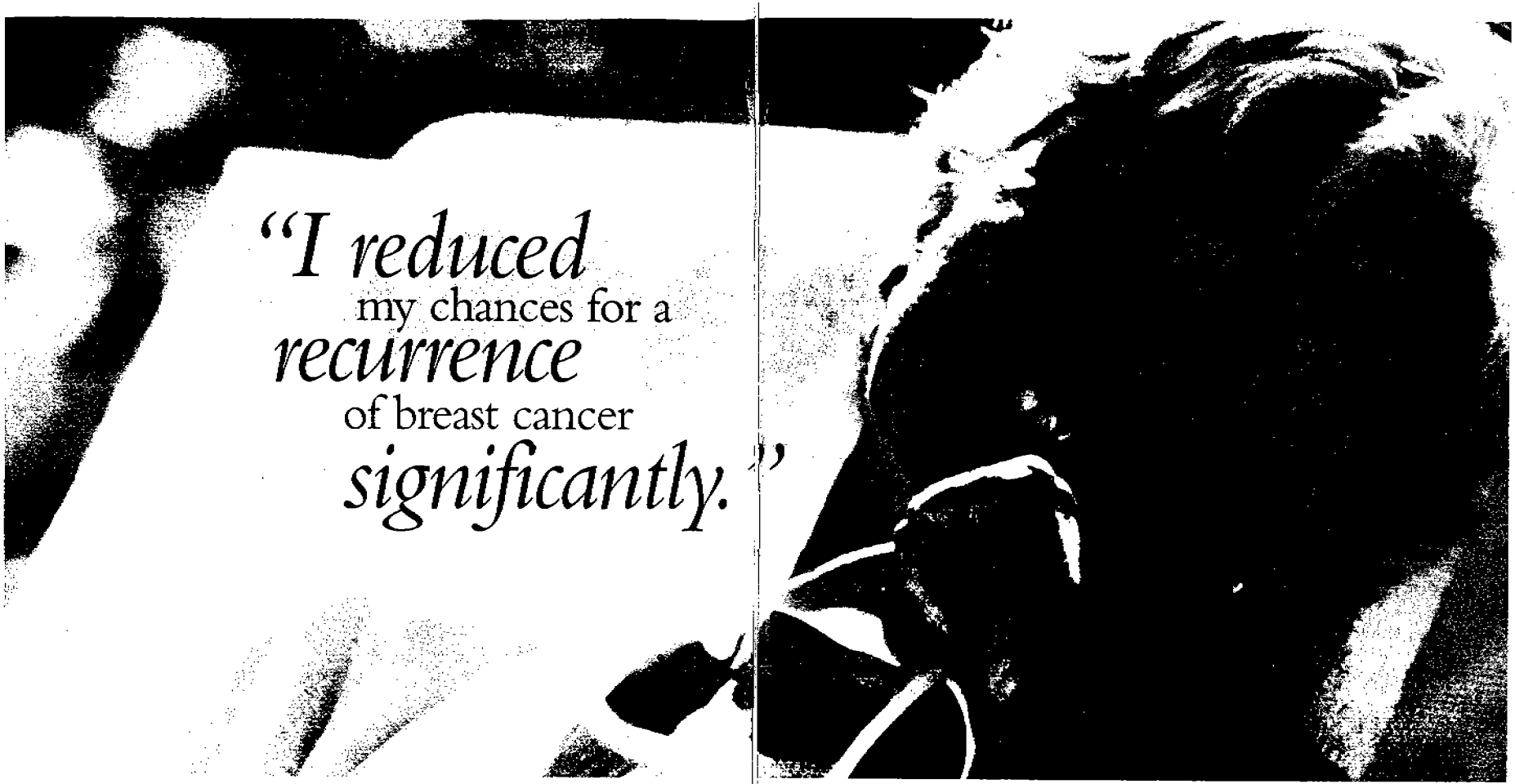
{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Grillo
12/14/01 11:20:40 AM



"I reduced my chances for a *recurrence* of breast cancer *significantly.*"

Ask your doctor about using 5-year NOLVADEX® (tamoxifen citrate) therapy.

More than ever before, women are facing breast cancer and winning due to advances in medicine and informed choices. But perhaps one of the most remarkable and exciting pieces of news for breast cancer survivors today is the result of the Peto Worldwide Overview. This Overview has proven that certain survivors can reduce their risk of breast cancer recurrence significantly if they take prescription Nolvadex for five years.[1]

5 years gives the most benefits in reducing recurrence.

In the Overview, one and two years of Nolvadex reduced breast cancer recurrence by 18% and 25%, respectively; five years reduced breast cancer recurrence by 42%. For women who are estrogen receptor (ER) positive status or estrogen receptor (ER) unknown, five years reduced their recurrence by 47%. In women who are ER negative, 5 years of Nolvadex reduced recurrence by 6% with no survival benefit.[1]

Nolvadex reduces recurrence in the opposite breast.

Major findings from the Overview prove that five years of Nolvadex reduces the incidence of new cancers in the opposite breast by 47%.[1]

Improves 10-year survival.

Five years of Nolvadex improves your 10-year survival regardless of your age, your menopausal status, or whether or not your lymph nodes were involved. However, Nolvadex is not indicated for women who are both premenopausal *and* node positive.

Possible side effects.

Nolvadex is not for all women. In general, most side effects were hormonal in nature: hot flashes, vaginal discharge, and irregular periods. Most were considered relatively mild, and very few women—5%—discontinued their therapy.[2]

More serious considerations are the increased frequency of changes in the uterine lining, including cancer. Women taking Nolvadex were two to four times more likely to develop uterine cancer or blood clots in the legs and lungs, although each of these occurred in less than 1% of women. Of course, any woman who's had a hysterectomy is not at risk for uterine cancer. **Pregnant women or women who are planning to become pregnant soon should not take Nolvadex;** premenopausal women taking Nolvadex should use an effective form of nonhormonal birth control.

Talk to your doctor.

Because the Peto Overview findings are so significant, every woman who's had breast cancer is urged to talk to her doctor about five-year therapy with Nolvadex. If you've taken Nolvadex for less than five years or not at all, speak with your doctor. Discussing these new findings is an important step for your future breast health care.

www.nolvadex.com

1. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998;351:1451-1467. 2. Nolvadex prescribing information, AstraZeneca LP, Wilmington, Delaware.

Please see important information on adjacent page.

NL1298

TABLETS
Nolvadex®
TAMOXIFEN CITRATE