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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

17-970/S-049 FA, 051

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-970/S-049 FA
NDA 17-970/S-051

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Laura Garcia-Davenport
Associate Director, Regulatory Affairs

Dear Ms. Davenport:

Please refer to your supplemental new drug application dated July 15, 2002, received July 16, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nolvadex (tamoxifen citrate) Tablets.

We acknowledge receipt of your submissions to S-051 dated August 28 and October 23, 2002, received August 30 and October 24, 2002, respectively. We also acknowledge receipt of the final printed labeling (FPL) for S-049 submitted on June 20, 2002, received June 21, 2002. The FPL will be retained with your file.

This supplemental new drug application provides for updated FIGO substaging information in the **WARNINGS** section, **Effects on the Uterus- Endometrial Cancer and Uterine Sarcoma** subsection, as requested in the Approval letter for S-049 dated May 16, 2002.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the submitted labeling text and with the minor editorial revisions listed below.

1. As a reminder, the **WARNINGS** section, **Effects on the Uterus – Endometrial Cancer and Uterine Sarcoma** subsection, 3rd paragraph should read as follows in the final printed labeling (the October 23, 2002, did not contain some of the revisions that were submitted in the July 15, 2002 original submission):

   "In an updated review of long-term data (median length of total follow-up is 6.9 years, including blinded follow-up) on 8,306 women with an intact uterus at randomization in the NSABP P-1 risk reduction trial, the incidence of both adenocarcinomas and rare uterine sarcomas was increased in women taking NOLVADEX. During blinded follow-up, there were 36 cases of FIGO Stage I endometrial adenocarcinoma (22 were FIGO IA, 13 IB, and 1 IC) in women receiving NOLVADEX and 15 cases in women receiving placebo [14 were FIGO Stage I (9 IA and 5 IB), and 1 case was FIGO Stage IV]. Of the patients receiving NOLVADEX who developed

endometrial cancer, one with Stage IA and 4 with Stage IB cancers received radiation therapy. In the placebo group, one patient with FIGO Stage IB cancer received radiation therapy and the patient with FIGO Stage IVB cancer received chemotherapy and hormonal therapy. During total follow-up, endometrial adenocarcinoma was reported in 53 women randomized to NOLVADEX (30 cases of FIGO Stage IA, 20 were Stage IB, 1 was Stage IC, and 2 were Stage IIIC) and 17 women randomized to placebo (9 cases were FIGO Stage IA, 6 were Stage IB, 1 was Stage IIIC, and 1 was Stage IVB (incidence per 1,000 women-years of 2.20 and 0.71, respectively). Some patients received post-operative radiation therapy in addition to surgery. Uterine sarcomas were reported in 4 women randomized to NOLVADEX (1 FIGO IA, 1 FIGO IB, 1 FIGO IIA, and 1 FIGO IIIC) and one patient randomized to placebo (FIGO 1A); incidence per 1,000 women-years of 0.17 and 0.04, respectively. Of the patients randomized to NOLVADEX, the FIGO IA and IB cases were a MMMT and sarcoma, respectively; the FIGO II was a MMMT; and the FIGO III was a sarcoma) and the one patient randomized to placebo had a MMMT. A similar incidence in endometrial adenocarcinoma and uterine sarcoma was observed among women receiving NOLVADEX in five other NSABP clinical trials."

2. In the Patient Package Insert, **"What are the most important things I should know about NOLVADEX?"** subsection, 3rd paragraph, the word "women" (two occurrences) should be changed to "woman" for grammatical correctness.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted labeling (package insert and patient package insert submitted October 23, 2002). These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 17-970/S-051." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Richard Pazdur
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