DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-970/S-052
NDA 17-970/S-048 FA
NDA 17-970/S-050 FA
NDA 17-970/S-051 FA

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

Attention: E. Jane Valas, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Valas:

Please refer to your supplemental new drug application dated May 27, 2004, received June 1, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NOLVADEX® (tamoxifen citrate) Tablets.

We also acknowledge receipt of your submission dated August 20, 2003, received August 21, 2003, which provided final printed labeling (FPL) for supplements 048, 050, and 051. This FPL has been superseded by the labeling submitted with S-052 and will be retained with your file.

This supplemental new drug application provides for revisions to the package insert in response to the following postmarketing commitment S-040 (approved on October 29, 1998) listed below:

Commitment #3
Data from the following P-1 substudies should be submitted when available:

- NSABP P-1B, "Bone mineral density and biochemical marker study to determine the effect of tamoxifen on bone in premenopausal and postmenoausal women".

- NSABP P-1G, "A study of the association between inherited mutations and the effect of tamoxifen on breast cancer incidence".

- Dr. Krag's substudy, "The effect of tamoxifen on the hemostasis system in women without breast cancer: Implications for cardiovascular disease prevention and assessment of thrombotic risk".

A timetable for submission should be provided.

The above commitment has now been fulfilled.

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

1. In the **BOXED WARNING**, the incidence rate of uterine sarcoma for placebo is shown as 0.0, however, this should be corrected to 0.04 as was approved with S-051 on January 30, 2003. This should be corrected.

2. In the **CLINICAL STUDIES** section, **Table 3**, two typographical errors have been made (shown in **bold**) and should be corrected:

Type of Event	# of Events		Rate/1000 Women/Year		95% CI	
	Placebo	Nolvadex	Placebo	Nolvadex	RR	Limits
Underwent Cataract Surgery[8]	63	101	**2.83**	4.57	1.62	1.18-2.22
Underwent Cataract Surgery[9]	**1.29**	201	5.44	8.56	1.58	1.26-1.97

should be

Type of Event	# of Events		Rate/1000 Women/Year		95% CI	
	Placebo	Nolvadex	Placebo	Nolvadex	RR	Limits
Underwent Cataract Surgery[8]	63	101	**21.83**	4.57	1.62	1.18-2.22
Underwent Cataract Surgery[9]	**129**	201	5.44	8.56	1.58	1.26-1.97

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling (text for the package insert, text for the Medication Guide). 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 15 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-052." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submission dated April 30, 1998 (S-040). These commitments are listed below.

Commitment #1
Thromboembolic events are a significant risk for women taking tamoxifen. As discussed at Oncologic Drugs Advisory Committee and recommended by the Committee, the applicant should perform a study to evaluate the etiology of drug-related clotting events, including assays for Factor V Leiden and activated protein C resistance. The study protocol should be submitted for review prior to initiation.

Commitment #2
All participants on the NSABP P-1 trial should have long-term follow-up for the events of cancer (invasive breast, non-invasive breast, endometrial, and other cancer), death, stroke, deep vein thrombosis, and pulmonary embolism. Data should be submitted at least yearly.

Commitment #4
Provide the results of the ongoing NSABP central pathology review, to include tumor grade as well as any other analyses you perform. These results can be provided on a rolling basis by category (for example, breast cancers, endometrial cancers, etc.). Provide the anticipated timetable for submission.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

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, HFD-410
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

Enclosure

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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