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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

17-970/S-049 FA, 051

Medical Review(s)

Medical Reviewer: Labeling supplement

NDA:	17-970	**Submission:**	SLR-049
Drug:	Tamoxifen	**Letter Date:**	April 18, 2002
Sponsor:	AstraZeneca	**Review Date:**	May 8, 2002 (received by PM 4/29/02)

This labeling supplement addresses all outstanding labeling changes from S-044 and S046 and consolidates them into SLR-049. The changes include changes to the adverse event listings submitted by the sponsor and changes to incorporate uterine sarcoma information requested by the Division.

In order to take an action on this supplement, which contains changes pending since 1999, review comments were sent to the sponsor by fax. Replies were submitted via fax and changes/agreements were incorporated into the labeling. The following review contains the initial review, then notes the sponsor's reply in each section. Please see the project manager's labeling review and the Action Letter for this supplement.

Required Regulatory Actions:

The project manager should convey the following comments to the sponsor via facsimile.

Comments to the sponsor:

1. Changes originally submitted in SLR-044 6/24/99 and 2/25/00: approved

a. The Division approves the changes made for Headaches, Cataracts, Hypertriglyceridemia, and Pancreatitis in ***Adverse Events—Postmarketing Experience.***

b. You have agreed to our recommendations for angioedema and the changes as written are approved in the PI (***Adverse Events—Postmarketing Experience).***

c. You agreed to delete "As with other additive hormonal therapy..." in ***WARNINGS—Effects on the Uterus—Endometrial Cancer and Uterine Sarcoma***. This phrase was appropriately deleted in the current supplement.

d. The changes made to the ***CLINICAL PHARMACOLOGY*** section (***Absorption and Distribution, Metabolism, Excretion, Special Populations, and Drug-drug Interactions***) were previously reviewed and are approved in this supplement.

e. The addition of "or any of its ingredients" to the ***CONTRAINDICATIONS*** section is approved.

f. The changes to ***Pregnancy Category D*** are approved as written.

g. The changes to ***Information for Patients—Reduction in Breast Cancer Incidence in High Risk Women*** are acceptable.

h. Changes to the ***Geriatric Use*** section are acceptable as written.

Reviewer Comment:

(1) The sponsor acknowledged these approvals in a fax dated 5/15/02.

2. Changes originally submitted in SLR-044 6/24/99 and 2/25/00: not approved as written

a. Warnings—Non-Malignant Effects on the Uterus

You did not add "Nolvadex has been reported to cause menstrual irregularity or amenorrhea."as requested 7/99 and 6/00. Support for this statement is included in submission P-022 (6/28/99), volume 137.1, section 4.4, page 10 and is mentioned in the PPI. The current supplement contains this line as a strike-out; it should be included in the final printed labeling.

b. Changes to Carcinogenesis, Mutagenesis, Impairment of Fertility

Your proposed labeling is not approved:

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As previously communicated to you, you should not include the comparison to toremifene. As written by the pharmacology reviewer, the labeling should read as:

"However, increased levels of DNA adducts were observed by 32P post-labeling in DNA from rat liver and cultured human lymphocytes."

c. Pulmonary events

As communicated 7/99 and 6/00, the Periodic Safety Update notes that the association of interstitial pneumonitis with tamoxifen is under investigation (P-022, volume 137.1, page 73, section 9.5). You have not provided a timetable for completing this evaluation and submitting potential labeling changes.

Reviewer Comments (from sponsor's fax dated 5/15/02):

(1) The sponsor agreed to add the requested statement to Warnings—Non-malignant effects on the uterus.

(2) The sponsor agreed to reinstate the FDA pharm-tox reviewer's statement.

(3) The sponsor submitted a justification document for analysis of cases of interstitial pneumonitis reported for tamoxifen. The proposed labeling, added to the Adverse Events—Postmarketing Experience" reads "Very rare reports of...interstitial pneumonitis, and rare reports of...". The labeling is acceptable as written.

3. Changes submitted in SNC to SEI-046 and current supplement (uterine sarcoma): Approved

The following changes are approved as written in the current supplement:

- You have appropriately moved the Black Box Warning to the beginning of the label
- The Black Box has an appropriate heading for women with DCIS and women at high risk for breast cancer
- Tables 1 and 3, as requested by the Division, contain information about all uterine cancers and sublines detailing cases of adenocarcinoma and cases of sarcoma
- The Indications and Usage sections for DCIS and Reduction in breast cancer incidence in high risk women appropriately refer the reader to the Black Box

- The Black Box warning contains the requested language (applies to all women; documents source of the rates; states that some events may be fatal; correct context for risk/benefit discussion; benefits outweigh risks in women with breast cancer) and the correct rates in the correct format for uterine malignancies, stroke, and pulmonary emboli
- We previously agreed that it was acceptable to use "uterine malignancies" in place of "uterine cancer"
- You have specified the length of follow-up from NSABP P-1 used to calculate uterine malignancy rates and corrected the number of patients included in the analysis—accepted
- You added "In the P-1 trial" in WARNINGS—Effects on the Uterus—Endometrial Cancer and Uterine Sarcoma" before the information on endometrial sampling. This modifier is acceptable.
- You added "There is evidence of an increased incidence..." under Thromboembolic Effects of Nolvadex. This addition is acceptable.
- The reference to the ADVERSE REACTIONS section in the Drug/Laboratory Testing Interactions section is acceptable.

Reviewer Comment:

(1) The sponsor acknowledged these approvals in a fax dated 5/15/02.

4. Changes submitted in SNC to SEI-046 and current supplement (uterine sarcoma): Not approved as written

a. You reinstated the general FIGO staging for uterine adenocarcinomas but you did not reinstate the subcategories (IA, IB, IC) as approved in the original labeling for the reduction in incidence indication.

b. You should submit the FIGO stage and substage for the 3 cases of uterine adenocarcinoma identified in P-1 participants since the reduction in incidence indication was approved.

c. You should submit information on how many of these patients received postoperative radiotherapy. The statement "some patients received post-operative radiation therapy in addition to surgery" should be evaluated using this information.

d. You removed the statement about anticoagulation in P-1 participants from the Drug Interactions section. It should remain in both this section and the Contraindications section. The other changes in the Drug Interactions section are acceptable as written.

Reviewer Comment (sponsor's fax dated 5/15/02)

(1) The sponsor agreed to the changes in d.

(2) For comments a, b, and c, the sponsor stated that this information for all detected cases was requested from the NSABP April 5, 2002. However, they have not received the information from NSABP to date. The sponsor should reinstate the FIGO substaging as originally written in the approved product labeling (see section 5). The sponsor should commit to submitting the updated FIGO substaging in a labeling supplement within 2 months.

Sponsor's facsimile dated May 15, 2002 (3 pm): The sponsor commits to submitting the information within 2 months.

5. WARNINGS—Effects on the Uterus—Endometrial Cancer and Uterine Sarcoma

Please see section 4 for comments about FIGO staging, substaging, and therapy. As currently written, this section is confusing. It begins by noting that tamoxifen increases the risk of uterine malignancy, both adenocarcinoma and sarcoma. Rates for both from P-1 are presented. A general warning is given about work-up of signs and symptoms. The following paragraph then reverts to older information about "uterine cancer" without distinguishing subtype. The final paragraphs then once more refer to P-1 and discuss only adenocarcinoma.

This section should be re-written in a clear logical orderly fashion.

Reviewer Comment:

(1) The sponsor submitted a rewritten section. In the new section, information from the Swedish trial and from NSABP B-14 was deleted. This deletion is acceptable, because more accurate information about incidence, rates, and outcome was derived from NSABP P-1 (8306 women with an intact uterus in a randomized double-blinded placebo-controlled study) and information derived from B-14 is incorporated into new language derived from analysis of all NSABP placebo-controlled blinded treatment trials of tamoxifen.

(2) The sentence "Most of the uterine cancers were diagnosed at an early stage, but deaths from uterine cancer have been reported" was deleted. It was replaced by "Some of the uterine malignancies (endometrial carcinoma or uterine sarcoma) have been fatal." This change is approved as written. The new warning is consistent with the language in the Black Box warning.

(3) The sponsor should reinstate the FIGO substaging in this section. After the first sentence in the second paragraph of Warnings—Effects on the Uterus—Endometrial Cancer and Uterine Sarcomas ("In the NSABP P-1 trial, among participants randomized to Nolvadex there was...95% CI: 1.27-4.92"), the sponsor should add "The 33 cases in participants receiving Nolvadex were FIGO Stage I, including 20 IA, 12 IB, and 1 IC endometrial adenocarcinomas. In participants randomized to placebo, 13 were FIGO Stage I (8 IA and 5 IB) and 1 was FIGO Stage IV. Five women on Nolvadex and 1 on placebo received postoperative radiation therapy in addition to surgery."

Sponsor fax 5/15/02 3 pm: The sponsor agrees to reinstate the above wording.

6. Dear Doctor letter

The Dear Doctor letter is acceptable as written.

Reviewer Comment:

(1) The proposed addition to the Dear Doctor letter is acceptable (fax 5/15/02).

Sponsor fax 5/15/02 3 pm: The sponsor acknowledges the approval.

7. MediGuide

You included a MediGuide in this submission. Your request to create a Medication Guide for tamoxifen is under review in a separate labeling supplement. The Patient Package Insert is an approved part of product labeling. You should withdraw the Mediguide and submit an updated version of the PPI for review.

Reviewer Comment:

(1) The sponsor withdrew the Medication Guide on May 14, 2002 via facsimile. The PPI was submitted via fax on 5/15/02. A separate review follows.

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/

Grant Williams, M.D.
Deputy/Team Leader

Medical Reviewer: Labeling supplement

NDA:	17-970	**Submission:**	SLR-049
Drug:	Tamoxifen	**Letter Date:**	April 18, 2002
Sponsor:	AstraZeneca		May 15, 2002 (PPI)
Review Date:	May 8, 2002		

The sponsor withdrew the Mediguide for tamoxifen and send an updated PPI for review. The following review addresses changes to the PPI.

I. Changes to the PPI—Approved

The following changes to the PPI are acceptable as written:

A. Changes to "What are the most important things I should know about Nolvadex?

1. From "Nolvadex can, however, also increase the risk of some serious and potentially life-threatening conditions, including uterine cancer, blood clots, and stroke" to "For all women, Nolvadex can, however, also increase the risk of some serious and potentially life-threatening - events, including uterine cancer, blood clots, and stroke. Some of these events have caused death." Acceptable as written

2. You direct women to discuss risks and benefits with their health care providers. The PI directs health care providers to discuss risks and benefits with their patients. Given the audiences for each part of the label (PI and PPI), this difference is appropriate and acceptable as written.

3. The strike-out on the first page of the PPI ("If you experience symptoms of any of these...") is acceptable.

B. Changes to "What is Nolvadex?"

The minor editorial changes in this section are approved.

C. Changes to "How does Nolvadex work?"

The clarification that the use of anticoagulants is a contraindication only for high-risk women is acceptable as written.

D. "What should I avoid or do while taking Nolvadex?"

The addition of "or have previously taken Nolvadex" (2 locations) is approved as written.

E. "What are the possible side effects of Nolvadex?"

The addition of references to the "body" of the uterus in addition to the "lining" of the uterus is acceptable.

The indication that uterine symptoms may be "life-threatening" is appropriate and approved as written.

Sponsor fax 5/15/02 3 pm: The sponsor acknowledges the Division's approval.

II. Changes to the PPI—Not approved

A. "What is Nolvadex?"

Please re-order this section. You address women at high risk for breast cancer, then women and men with advanced breast cancer, then women with DCIS, then early stage breast cancer. Given that the focus of the PPI is for high-risk women, the reviewer suggests information for high-risk women, then women with DCIS, then women with early stage breast cancer, then women with advanced disease.

Sponsor fax 5/15/02 3 pm: The sponsor agrees to re-order this section.

B. "What are the possible side effects of Nolvadex?"

You did not comply with recommendations for angioedema in the PPI. As written in July 1999 and June 2000:

Patient Package Insert, "What are the possible Side Effects of Nolvadex?", current:
"Stop taking Nolvadex and contact your doctor immediately if you develop angioedema (swelling of the face, lips, tongue, and/or throat)."

Add: "...even if you have been taking tamoxifen for a long time." (PPI)

Justification: The statement for the PI is taken from the Justification Document, tab 3 and has been modified for the PPI. It will alert physicians and patients to the potentially long delay in the manifestation of this event relative to the initiation of tamoxifen treatment.

The PPI does not contain the statement "even if you have been taking tamoxifen for a long time."

Sponsor fax 5/15/02 3 pm: The sponsor agrees to insert this phrase.

C. Changes relevant to several sections

You did not add the following to the PPI as requested 7/99 and 6/00:

Current: "You should not become pregnant when taking Nolvadex or during the two months after you stop taking it as Nolvadex may harm your unborn child. Please contact your doctor for birth control recommendations."

Add: "Tamoxifen does not prevent pregnancy, even in the presence of menstrual irregularity." to the sections **Who should not take Nolvadex?**, **Are there other important factors to consider before taking Nolvadex?**, and **What should I avoid/or do while taking Nolvadex?** after the above statements.

Justification: See **Pregnancy Category D**

Sponsor fax 5/15/02 3 pm: The sponsor agrees to make the requested changes.

III. Recommendations, not requirements

A. "How should I take Nolvadex?"

You present dosing information first for patients with breast cancer, second for women at high risk. You may wish to reverse the order so that information for high-risk women is consistently presented first throughout the document.

Sponsor fax 5/15/02 3 pm: The sponsor agrees to re-order this section.

IV. Addendum

The PM review on 5/15/02 determined that the sponsor deleted the table of tamoxifen's risks and benefits from the PPI. This table must be reinstated.

Sponsor communication by telephone 5/16/02: They commit to reinstating the table.

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/

Grant Williams, M.D.
Team Leader

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

/s/

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