CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

17-970/S-049 FA, 051

Administrative Documents

DIVISION OF ONCOLOGY DRUG PRODUCTS
CSO LABELING REVIEW

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

DRUG: Nolvadex (tamoxifen citrate) Tablets

SPONSOR: AstraZeneca Pharmaceuticals

SUBMISSION INFORMATION:

Submission number	Date of submission	Receipt date of submission
S-049 FA	June 20, 2002	June 21, 2002
S-051	July 15, 2002	July 16, 2002
S-051 BL	August 28, 2002	August 30, 2002
S-051 BL	October 23, 2002	October 24, 2002

BACKGROUND:

S-049 FA provides final printed labeling (FPL) in response to the May 16, 2002, Approval letter for S-049.

S-051 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. Both labeling amendment submissions provide for further revisions to the labeling in response to FDA comments conveyed during the review of this supplement.

I compared the proposed FPL for S-049 to the labeling that was approved for S-049 on May 16, 2002. I also compared the FPL for S-049 and the proposed labeling for S-051 (and all amendments) to the most recently approved labeling for S-050 dated August 30, 2002. Any changes and/or discrepancies are outlined below.

DISCUSSION:

1. In the **CLINICAL PHARMACOLOGY** section, **Clinical Studies – Reduction in Breast Cancer Incidence in High Risk Women** subsection, **Table 3: Major Outcomes of the NSABP P-1 Trial**, the last footnote has been changed as follows:

   "[10]Updated long-term follow-up data (median 6.9 years) added after cut-off for the other information in this table."

   has been changed to

"[10]Updated long-term follow-up data (median 6.9 years) from NSABP P-1 study added after cut-off for the other information in this table."

Comment: This change was reviewed by Dr. Susan Honig on May 9, 2002, and was found to be acceptable. See Dr. Honig's review dated May 16, 2002.

2. In the **WARNINGS** section, **Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma** subsection, the third paragraph was revised as follows:

"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). 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). 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 0 patients randomized to placebo (incidence per 1,000 women-years of 0.17 and 0.0, respectively). A similar incidence in endometrial adenocarcinoma and uterine sarcoma was observed among women receiving NOLVADEX in five other NSABP clinical trials."

Comment: In the approval letter for S-049 dated May 16, 2002, the Division recommended that the sponsor provide updated FIGO substaging information for the three additional cases on tamoxifen and the one additional case on placebo identified during blinded follow-up of NSABP P-1. This text was submitted with S-051 on July 15, 2002. On July 25 and August 22, 2002, the following comment was sent to the sponsor:

"The fax contains the FIGO substaging for patients diagnosed with uterine cancer during blinded follow-up of NSABP P-1. However, it does not contain the number of the patients on each arm, by FIGO substage, who required radiotherapy. This information was requested in the approval letter for S-049. Please submit the information on radiotherapy ASAP in order to complete our review of this labeling change."

*In response to this comment, on August 28, 2002, the sponsor submitted revised wording for the **WARNINGS** section, **Effects on the Uterus – Endometrial Cancer and Uterine Sarcoma** subsection, 3rd paragraph as follows:*

"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, 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 (1 FIGO IA, 1 FIGO IB, 1 FIGO IIA, and 1 FIGO IIIC). 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 0 patients randomized to placebo (incidence per 1,000 women-years of 0.17 and 0.0, respectively). A similar incidence in endometrial adenocarcinoma and uterine sarcoma was observed among women receiving NOLVADEX in five other NSABP clinical trials."

After review of these proposed revisions, the Division sent the sponsor the following comment by fax on September 27, 2002:

"In supplement 051, you submitted labeling to provide updated FIGO substaging information and the number of patients with uterine cancer who required radiotherapy as per FDA request. Your submitted labeling notes that a patient in the placebo group received chemotherapy and hormonal therapy, but it does not mention the use of radiotherapy in this group.

The previously approved labeling stated: 'Five women receiving NOLVADEX and 1 receiving placebo with FIGO Stage IB disease received postoperative radiation therapy in addition to surgery.'

Please clarify why you have deleted the reference to radiotherapy in the placebo patient with FIGO Stage IB disease. If the deletion was an error, please submit an amendment to SLR-051 as soon as possible."
On October 23, 2002, the sponsor submitted an amendment to S-051. The sponsor noted that the language regarding radiotherapy for the placebo patient was located

*in the 2nd paragraph of the same section. The amendment also provided for the following revisions to the **WARNINGS** section, **Effects on the Uterus – Endometrial Cancer and Uterine Sarcoma** subsection, 3rd paragraph:*

"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. 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). Of the patients receiving NOLVADEX who developed endometrial cancer, one with Stage IA and 4 with Stage IB cancers received radiation therapy. In the plabeco group, one patient with FIGO Stage IB cancer received radiation therapy and the patient with FIGO Stage IVB cancer received chemotherapy and hormonal therapy. Uterine sarcomas were reported in 4 women randomized to NOLVADEX (1 was FIGO IA, 1 was FIGO IB, 1 was FIGO IIA, and 1 was FIGO IIIC) and one patient randomized to placebo (FIGO IA); 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 1 patient randomized to placebo had a MMMT). A similar increased incidence in endometrial adenocarcinoma and uterine sarcoma was observed among women receiving NOLVADEX in five other NSABP clinical trials."

This revised text was reviewed by Dr. Susan Honig and was found to be acceptable. However, it is noted that some of the proposed text from the initial submission dated July 15, 2002. The sentence, "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). During total follow-up, endometrial..." should be reinstated into the paragraph.

3. In the **BLACK BOX WARNING**, the incidence of uterine sarcoma for the placebo group was revised from 0.0 per 1,000 women-years to 0.04 per 1,000 women-years.

Comment: This change was submitted with SLR-051 BL dated October 23, 2002. It was reviewed by Dr. Susan Honig and was found to be acceptable.

4. In the **CLINICAL PHARMACOLOGY** section, a **Pediatric Patients** subsection has been added.

   Comment: This section was submitted with S-050 and was approved by the Division of Metabolic and Endocrine Drug Products on August 30, 2002.

5. In the **CLINICAL PHARMACOLOGY** section, a **Clinical Studies- McCune-Albright Syndrome** subsection has been added.

   Comment: This section was submitted with S-050 and was approved by the Division of Metabolic and Endocrine Drug Products on August 30, 2002.

6. In the **PRECAUTIONS** section, the **Pediatric Use** subsection has been changed as follows:

   from "The safety and efficacy of NOLVADEX in pediatric patients have not been established."

   to "**The safety and efficacy of NOLVADEX for girls aged two to 10 years with McCune-Albright Syndrome and precocious puberty have not been studied beyond one year of treatment. The long-term effects of NOLVADEX therapy for girls have not been established.** In adults treated with NOLVADEX, an increase in the incidence of uterine malignancies, stroke and pulmonary embolism has been noted (see **BOXED WARNING**, and **CLINICAL PHARMACOLOGY – Clinical Studies –McCune-Albright Syndrome** subsection)."

   Comment: This section was changed with S-050 and was approved by the Division of Metabolic and Endocrine Drug Products on August 30, 2002.

7. In the **ADVERSE REACTIONS** section, a subsection titled, "**Pediatric Patients – McCune-Albright Syndrome**" has been added.

   Comment: This section was added with S-050 and was approved by the Division of Metabolic and Endocrine Drug Products on August 30, 2002.

8. In the Patient Package Insert, **"What are the most important things I should know about NOLVADEX?"** subsection, 3rd paragraph, the word "woman" has been changed to "women".

   Comment: This change appears to be a typographical error and should be changed back to "woman" so that the sentence reads, "If you are a woman at high risk for breast cancer or a woman with DCIS considering..."

9. In the Patient Package Insert, **"Who should not take NOLVADEX?"** section, the last bullet has been modified as follows:

from "Children should not take NOLVADEX because treatment for them has not been sufficiently studied."

to "Girls with McCune-Albright Syndrome (a genetic condition associated with premature puberty) under the age of two and older than 10 years of age should not take NOLVADEX because treatment in this age group has not been studied. NOLVADEX has not been studied in boys."

Comment: This change was made with S-050 and was approved by the Division of Metabolic and Endocrine Drug Products on August 30, 2002.

RECOMMENDATIONS:
Acceptability of these changes is indicated by the concurrences below. With these concurrences, an ACKNOWLEDGE AND RETAIN letter will issue for NDA 17-970/S-049 FA and an APPROVAL letter will issue for NDA 17-970/S-051, requesting FPL identical to the October 23, 2002 draft labeling with minor editorial changes.

/S/

Christy Wilson
Consumer Safety Officer

concurrence: /S/

Dotti Pease
Chief, Project Management Staff

concurrence: /S/

Susan Honig, M.D.
Medical Officer

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/s/

Christy Cottrell
1/28/03 03:36:25 PM
CSO
DDR: Please use this review to close out the open assignments to both the CSO and Medical Officer.

Dotti Pease
1/30/03 01:15:22 PM
CSO

Christy Cottrell
4/16/03 03:57:47 PM
CSO

FAX

FOOD AND DRUG ADMINISTRATION
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To: Laura Garcia-Davenport	**From:** Christy Wilson
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Phone: (302) 885-7533	**Phone:** (301) 594-5761
Pages, including cover sheet: 1	**Date:** 9-27-02

Re: NDA 17-970 for Nolvadex- supplement 051

Laura,

Please refer to your NDA 17-970 for Nolvadex, specifically, supplement 051. Included in this fax is a comment from the Medical Officer.

- In supplement 051, you submitted labeling to provide updated FIGO substaging information and the number of patients with uterine cancer who required radiotherapy as per FDA request. Your submitted labeling notes that a patient in the placebo group received chemotherapy and hormonal therapy, but is does not mention the use of radiotherapy in this group.

  The previously approved labeling stated:
  "Five women receiving NOLVADEX and 1 receiving placebo with FIGO Stage IB disease received postoperative radiation therapy in addition to surgery."

  Please clarify why you have deleted the reference to radiotherapy in the placebo patient with FIGO Stage IB disease. If the deletion was an error, please submit an amendment to SLR-051 as soon as possible.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Wilson

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/s/

Christy Wilson
9/27/02 02:18:23 PM
CSO

FAX

FOOD AND DRUG ADMINISTRATION
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Re: NDA 17-970 for Nolvadex, specifically, supplement 049 submission dated 7-15-02

Laura,

Please refer to your NDA 17-970 for Nolvadex, specifically, your submission to S-049 dated July 15, 2002 in which you submitted the requested updated FIGO staging for the patients diagnosed with uterine cancer during blinded follow-up in the P-1 study. In a fax dated July 25, 2002, we sent the following comment from the Medical Officer:

- The fax contains the FIGO substaging for patients diagnosed with uterine cancer during blinded follow-up of NSABP P-1. However, it does not contain the number of the patients on each arm, by FIGO substage, who required radiotherapy. This information was requested in the approval letter for S-049. Please submit the information on radiotherapy ASAP in order to complete our review of this labeling change.

We have not yet received a response to this comment. Please submit your response as soon as possible, or provide an estimated timeframe for submission. If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Wilson

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/s/

Christy Wilson
8/23/02 09:43:03 AM
CSO

FAX

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Re: NDA 17-970 for Nolvadex, specifically, supplement 049

Patricia,

Please refer to your NDA 17-970 for Nolvadex, specifically, supplement 049 dated April 18, 2002. This fax serves as a reminder of your commitment to provide updated FIGO staging/substaging and treatment for all patients diagnosed with uterine cancer during the updated P-1 analysis by July 15th. This commitment was a condition of the approval of S-049.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Wilson

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/s/

Christy Wilson
8/26/02 01:56:23 PM
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Pages, including cover sheet: 2	**Date:** 5-15-02

Re: NDA 17-970 for Nolvadex, specifically, supplement 049

Patricia,

Please refer to your NDA 17-970 for Nolvadex, specifically supplement 049 dated April 18, 2002. We also refer to FDA faxes dated May 10, 14, and 15, 2002 conveying comments from the review team. We acknowledge receipt of a fax from AstraZeneca on May 10, 2002 providing the Patient Package Insert and two faxes from AstraZeneca dated May 15, 2002, which provide responses to the Division's comments. It is understood that official copies of the faxed correspondence will be submitted officially to the file for NDA 17-970.

Based upon your May 15, 2002 agreements to incorporate all changes to the labeling as requested by the Division, we intend to approve S-049 tomorrow, May 16, 2002. In order for you to prepare for distribution of the labeling and Dear Doctor letter at the ASCO meeting, the Division hereby agrees that you may initiate printing of the labeling today. We intend to issue an approval letter tomorrow to be accompanied by a clean copy of the labeling and Patient Package Insert.

Please submit to the Division no later than 8:00 am tomorrow morning, an electronic Word version of the final labeling that you have sent for printing. Prior to issuing the approval letter, the Division will conduct an electronic Word comparison between our labeling for the letter and your labeling for printing, and ensure that they are identical. If any discrepancies are found during this comparison, we will note them in the approval letter and request that the labeling be corrected as soon as possible.

If you have any questions, please call me at (301) 594-5761.

Thanks,

Christy Wilson

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/s/

Christy Wilson
5/16/02 11:43:27 AM
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FAX

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Pages, including cover sheet: 4	**Date:** 5-15-02

Re: NDA 17-970 for Nolvadex, specifically, supplement 049

Patricia,

Please refer to your NDA 17-970 for Nolvadex, specifically, supplement 049 dated April 18, 2002. Please see the following comments from the clinical reviewer regarding your May 15th response to our prior comments conveyed by facsimile transmission on May 10 and 14, 2002.

1. **Regarding Item 2c Pulmonary Events:** 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 section reads, "Very rare reports of...interstitial pneumonitis, and rare reports of...". The labeling is acceptable as written.

2. **Regarding Item 4 Uterine sarcoma:** 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.

3. **Regarding Item 5 Warnings – Effects on the Uterus – Endometrial Cancer and Uterine Sarcoma:**

   a. 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.

   b. 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.

   c. 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."

4. **Regarding the Dear Doctor letter:** The proposed addition to the Dear Doctor letter is acceptable.

5. **Regarding the Patient Package Insert (PPI):** The following changes to the PPI are acceptable as written.

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

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

   b. 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.

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

Changes to **"What is Nolvadex?":** The minor editorial changes in this section are approved.

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.

Changes to **"What should I avoid or do while taking Nolvadex?":** The addition of "or have previously taken Nolvadex" (2 locations) is approved as written.

Changes to **"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.

6. **Regarding the Patient Package Insert (PPI):** The following changes to the PPI are not approved as written.

Changes to **"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.

Changes to **"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."

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**

7. **Recommendations, not requirements:**

Regarding **"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.

Please fax your response to these comments to my attention at (301) 594-0499, as soon as possible, but no later than 4:00 pm today, if an action if expected this afternoon. If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Wilson

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/s/

Christy Wilson
5/16/02 11:39:49 AM
CSO

FAX

FOOD AND DRUG ADMINISTRATION
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Pages, including cover sheet: 2	**Date:** 5-14-02

Re: NDA 17-970 for Nolvadex, specifically, supplement 049

Patricia,

Please refer to your NDA 17-970 for Nolvadex, specifically, supplement 049 dated April 18, 2002. Please see the following comments from the review team regarding some of the proposed labeling changes:

1. In the **WARNINGS** section, **Non-Malignant Effects on the Uterus** subsection, the following statement has been deleted:

   "NOLVADEX has been reported to cause menstrual irregularity or amenorrhea."

   Comment: The Medical Officer believes that this statement should remain in the labeling.

2. In the **WARNINGS** section, **Other Cancers** subsection, the term "non-uterine" has been deleted throughout the paragraph, when referring to other cancers.

   Comment: The Medical Officer believes that the term "non-uterine" should remain in this paragraph for clarity.

3. In the **PRECAUTIONS** section, **Drug Interactions** subsection, the statement, "In the NSABP P-1 trial, women who required coumarin-type anticoagulants for any reason were ineligible for participation in the trial (See CONTRAINDICATIONS)," has been deleted.

   Comment: The Medical Officer believes that this statement should remain in this section.

4. In the **PRECAUTIONS** section, **Mutagenesis** subsection, 2nd sentence:

   In a prior review, the Pharmacologist recommended the following wording:

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

   In S-049, you propose:

   [ ]

   Comment: The Pharmacologist believes the original, more generalized wording should remain in the labeling.

Please be reminded that review of the Patient Package Insert is still ongoing and additional comments may be forthcoming. We also acknowledge receipt of your request to withdraw the Medication Guide from S-049 and your intention to submit the Patient Package Insert officially as part of the S-049 submission.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Wilson

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/s/

Christy Wilson
5/15/02 09:23:17 AM
CSO

FAX

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Pages, including cover sheet: 4	**Date:** 5-10-02

Re: NDA 17-970 for Nolvadex, specifically, supplement 049

Patricia,

Please refer to your NDA 17-970 for Nolvadex, specifically, supplement 049 dated April 18, 2002. Attached are preliminary comments from the Medical Officer regarding this supplement. Project Manager and Pharmacologist labeling reviews, as well as the Division's review of the proposed revisions to the Patient Package Insert are still pending. Additional comments may be forthcoming early next week.

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.

b. 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.

c. 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.

d. You have agreed to our recommendations for angioedema and the changes as written are approved in the PI.

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

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

g. Changes to the Geriatric Use section are acceptable as written.

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

Package Insert

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

  Warnings—Non-Malignant Effects on the Uterus

  Add: "Nolvadex has been reported to cause menstrual irregularity or amenorrhea."

  Justification: 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.

- 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.

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

a. 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.

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.

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.

6. **Dear Doctor letter**

The Dear Doctor letter is acceptable as written.

Again, please note that these are preliminary comments from the Medical Officer only. Project Manager and Pharmacologist labeling reviews are still pending, as is the Division's review of the proposed revisions to the Patient Package Insert faxed to the Division on May 10, 2002. Additional comments may be forthcoming.

Additionally, as discussed in a telephone conversation today, AstraZeneca will need to submit a request to withdraw the Medication Guide submitted as part of S-049, and must instead submit the proposed Patient Package Insert. The Medication Guide
therefore the Division cannot approve S-049 so long as the Medication Guide is still part of the submission.

You may fax your response to these comments to my attention at (301) 594-0499. If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Wilson

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

/s/

Christy Wilson
5/15/02 09:10:57 AM
CSO